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Editor’s Foreword

From time to time we have devoted an entire issue of the Journal to one particularly controversial lead article, followed by interdisciplinary critiques of that article by knowledgeable commentators, and a rebuttal by the original author. Topics we have explored in this way include cross-cultural counseling for near-death experiencers (NDErs) (Fall 1987), an electromagnetic hypothesis on survival of bodily death (Winter 1987), a neurobiological model of NDEs (Summer 1989), a sociocultural understanding of NDEs (Winter 1991), a psychodynamic approach to NDEs and UFO abduction experiences (Summer 1994), and frightening NDEs (Fall 1994). In this issue, we continue this tradition with a discussion of a neurophysiological model of NDEs that has been floated in various medical journals for the past decade without adequate attention.

New Zealand neuropsychiatrist Karl Jansen, now working in England, leads off this issue with a detailed presentation of what he calls the “ketamine model” of NDEs, namely, that they result from blockade of the brain's N-methyl-D-aspartate (NMDA) receptors. While Jansen has argued for this model elsewhere, this article marshals all the theoretical reasoning, empirical evidence, and supportive analogies that render this hypothesis plausible. We follow Jansen’s article with critiques by psychiatrist Rick Strassman, who has pioneered the scientific study of ketamine and other hallucinogenic drugs; by British neuropsychiatrist and near-death researcher Peter Fenwick; by Russian psychiatrist Igor Kungurtsev, who developed the technique of ketamine-assisted death-rebirth therapy; by pediatrician and near-death researcher Melvin Morse; by psychiatrists and near-death researchers Stuart Twemlow and Glen Gabbard; and by Italian anesthesiologist and toxicologist Antonio Bianchi, who has studied the use of hallucinogenic drugs in death-rebirth rituals among African tribes. This issue concludes with Jansen’s response to these commentaries, in which he addresses the questions raised by our reviewers and discusses the possible evolutionary advantage of the ketamine/NDE mechanism.

Bruce Greyson, M.D.
The Ketamine Model of the Near-Death Experience: A Central Role for the N-Methyl-D-Aspartate Receptor

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ABSTRACT: Near-death experiences (NDEs) can be reproduced by ketamine via blockade of receptors in the brain for the neurotransmitter glutamate, the N-methyl-D-aspartate (NMDA) receptors. Conditions that precipitate NDEs, such as hypoxia, ischemia, hypoglycemia, and temporal lobe epilepsy, have been shown to release a flood of glutamate, overactivating NMDA receptors and resulting in neurotoxicity. Ketamine prevents this neurotoxicity. There are substances in the brain that bind to the same receptor site as ketamine. Conditions that trigger a glutamate flood may also trigger a flood of neuroprotective agents that bind to NMDA receptors to protect cells, leading to an altered state of consciousness like that produced by ketamine.

The near-death experience (NDE) is a phenomenon of considerable importance to medicine, neuroscience, neurology, and psychiatry (Greyson and Stevenson, 1980; Jansen, 1989a, 1989b, 1990b; Ring, 1980; Sabom, 1982; Stevenson and Greyson, 1979). Recent advances in neuroscience are bringing us closer to a scientific understanding of this intriguing altered state of consciousness. Irrespective of personal religious and philosophical beliefs, NDEs are not evidence for life after death on simple logical grounds: death is defined as the final, irreversible end. The Oxford English Dictionary (Sykes, 1982) refers to death as the “final cessation of vital functions” (italics added). Those who have “returned” did not, by definition, die, al-
though their minds, brains, and bodies may have been in a very unusual state. The theory developed in this paper makes no attempt to address religious beliefs about events after death, but does argue that persons who report NDEs have not died.

There is overwhelming evidence from thousands of studies relating brain events to alterations in mental state that "mind" results from neuronal activity. The dramatic effects on the mind of adding hallucinogenic drugs to the brain, and the religious experiences that sometimes result, provide further evidence for this (Grinspoon and Bakalar, 1979). Within a scientific paradigm, it is not possible that the "spirit rises out of the body, leaving the brain behind, but somehow still incorporating neuronal functions such as sight, hearing, and proprioception" (Morse, 1989, p. 225).

Features that have been associated with NDEs can be reproduced by the intravenous administration of 50 to 100 milligrams of ketamine (Collier, 1972; Domino, Chodoff, and Corssen, 1965; Ghoneim, Hinrichs, Mewaldt, and Peterson, 1985; Grinspoon and Bakalar, 1979; Jansen, 1989a, 1989b, 1990b, 1993; Lilly, 1978; Rogo, 1984; Rumpf, Pedick, Teuteberg, Munchhoff, and Nolte, 1969; Siegel, 1978, 1980, 1981; Sputz, 1989; Stafford, 1977; White, Way, and Trevor, 1982). There is increasing evidence suggesting that the reproduction of NDEs by ketamine is unlikely to be a coincidence. This evidence includes the discovery of the major neuronal binding site for ketamine, known as the phencyclidine (PCP) binding site of the N-methyl-D-aspartate (NMDA) receptor (Thomson, West, and Lodge, 1985); the importance of NMDA receptors in the cerebral cortex, particularly in the temporal and frontal lobes; the key role of these sites in cognitive processing, memory, and perception; their role in epilepsy, psychoses (Jansen and Faull, 1991), hypoxia/ischemia, and epileptic cell damage (excitotoxicity); the prevention of this damage by ketamine; the discovery of substances in the brain called "endopsychosins," which bind to the same site as ketamine; and the role of ions such as magnesium and zinc in regulating the site (Anis, Berry, Burton, and Lodge, 1983; Barnes, 1988; Ben-Ari, 1985; Benveniste, Drejer, Schousboe, and Diemer, 1984; Choi, 1988; Coan and Collingridge, 1987; Collingridge, 1987; Contreras, DiMaggio, and O'Donohue, 1987; Cotman and Monaghan, 1987; Jansen, 1989a, 1989b, 1990a, 1990b, 1991, 1993; Jansen and Faull, 1991; Jansen, Faull, and Dragunow, 1989; Jansen, Faull, Dragunow, and Leslie, 1991; Jansen, Faull, Dragunow, and Synek, 1990; Mody and Heinemann, 1987; Monaghan, Bridges, and Cotman, 1989; Nowak, Ber-
gestovski, Ascher, Herbet, and Prochiantz, 1987; Quirion, Chichepor-
tiche, Contreras, Johnston, Lodge, Tam, Woods, and Zukin, 1987; Quirion, DiMaggio, French, Contreras, Shiloach, Pert, Everist, Pert, and O'Donohue, 1984; Rothman and Olney, 1987; Simon, Swan, Griffi-
ths, and Meldrum, 1984; Sonders, Keana, and Weber, 1988; Thom-
son, 1986; Westbrook and Mayer, 1987).

Characteristic Features of the Near-Death Experience

There is no internationally determined and agreed upon set of cri-
teria that define the NDE, no list of “research diagnostic criteria”
similar to those provided by the American Psychiatric Association
(APA) for psychiatric disorders. This lack has allowed some critics
of neurobiological models to dismiss those models because some par-
ticular criterion they consider important was not fully accounted for
by the model being proposed, although it may well be that a consen-
sus, statistical definition of the key features of the NDE would
not include those features—just as, for example, the APA definition
of schizophrenia (American Psychiatric Association, 1994) repre-
sents an international consensus and avoids the sectarian views of a few,
or inclusion of obscure cases that do not meet the general rule.

For example, Glen Gabbard and Stuart Twemlow (1989) argued
that Juan Saavedra-Aguilar and Juan Gómez-Jeria’s neurobiological
hypothesis (1989), which was based on temporal lobe electrical ab-
normalities, did not have general validity because Gabbard and
Twemlow had identified five cases in which hypoxia and stress did
not appear to be a triggering factor. These cases are certainly not
adequate grounds for the dismissal of neurobiological models.

Ketamine administered by intravenous injection in appropriate
dosage can reproduce all the features of the NDE that have been
commonly described in the most cited works in this field (Collier,
1972; Domino, Chodoff, and Corssen, 1965; Ghoneim, Hinrichs, Me-
waldt, and Peterson, 1985; Grinspoon and Bakalar, 1979; Jansen,
1989a, 1989b, 1990b, 1991, 1993; Lilly, 1978; Rogo, 1984; Rumpf,
Pedick, Teuteberg, Munchhoff, and Nolte, 1969; Siegel, 1978, 1980,
1981; Sputz, 1989; Stafford, 1977; White, Way, and Trevor, 1982), and
the account outlined below is based upon these works and also upon
NDEs described to me. Unfortunately, the study in which persons
who have had NDEs are given ketamine and asked to compare the
two experiences has yet to be carried out. Information in this area remains anecdotal.

I have experienced several NDEs and have also been administered ketamine as an anesthetic and within experimental paradigms. The NDEs and the ketamine experiences were very similar. Ketamine produced effects that were like the NDEs described by Bruce Greyson and Ian Stevenson (1980), by Melvin Morse, Doug Conner, and Donald Tyler (1985), by Raymond Moody (1975), by Russell Noyes and Roy Kletti (1976a), by Kenneth Ring (1980), and by Michael Sabom (1982). Ketamine produced travel through a tunnel, emergence into the light, and a "telepathic" exchange with an entity that could be described as "God," although I have no religious beliefs and had no particular expectations on first experiencing the drug. Neither the NDEs nor the ketamine experiences bore any resemblance to the effects of psychedelic drugs such as dimethyltryptamine (DMT) and lysergic acid diethylamide (LSD), in contradistinction to a previous assertion by Scott Rogo that ketamine "induces a short psychedelic 'trip' resembling that induced by lysergic acid diethylamide (LSD)" (1984, p. 88).

Important features of NDEs include a sense that what is experienced is "real" and that one is actually dead, a sense of ineffability, timelessness, and feelings of calm and peace, although some cases have been frightening. There may be analgesia, apparent clarity of thought, a perception of separation from the body, and hallucinations of landscapes and beings such as "angels" or people, including partners, parents, teachers and friends (who may be alive at the time), and religious and mythical figures. Transcendent mystical states are commonly described. Memories may emerge into consciousness, and are sometimes organized into a "life review" (Greyson, 1983). Hearing noises during the initial part of the NDE has also been described (Greyson and Stevenson, 1980; Morse, Conner, and Tyler, 1985; Noyes and Kletti, 1976a; Osis and Haraldsson, 1977; Ring, 1980; Sabom, 1982).

Kenneth Ring (1980) classified NDEs on a five-stage continuum: (1) feelings of peace and contentment; (2) a sense of detachment from the body; (3) entering a transitional world of darkness (the "tunnel experience"); (4) seeing a bright light; and (5) "entering the light." Sixty percent of NDErs interviewed by Ring experienced stage 1, but only 10 percent attained stage 5 (Ring, 1980). As might be expected in a mental state with a neurobiological origin, more mundane accounts also occur, such as children who may "see" their schoolfellows rather than God and angels (Morse, Conner, and Tyler, 1985).
Ketamine and Phencyclidine

Ketamine, first synthesized in 1962 by Calvin Stevens (McCarthy, 1981), is a short-acting, hallucinogenic, dissociative anesthetic related to phencyclidine (PCP). Both ketamine and PCP are arylcyclohexylamines; they are not opioids and are not related to LSD. In contrast to PCP, ketamine is relatively safe, an uncontrolled drug in most countries, and is used as an anesthetic for children (White, Way, and Trevor, 1982). Anesthetists attempt to prevent patients from having NDEs or "emergence phenomena" by the co-administration of benzodiazepines and other sedative substances that produce "true" unconsciousness rather than dissociation (Reich and Silvay, 1989).

Ketamine produces an altered state of consciousness that is very different from that of "psychedelic" drugs such as LSD (Grinspoon and Bakalar, 1979). As noted in the references cited above, it can reproduce all features of the NDE, including travel through a dark tunnel into light, the conviction that one is dead, apparent "telepathic communion with God," hallucinations, out-of-body experiences, and mystical states. If given intravenously, it has a brief action with an abrupt end. Lester Grinspoon and James Bakalar wrote of

becoming a disembodied mind or soul, dying and going to another world. Childhood events may also be re-lived. The loss of contact with ordinary reality and the sense of participation in another reality are more pronounced and less easily resisted than is usually the case with LSD. The dissociative experiences often seem so genuine that users are not sure that they have not actually left their bodies. (1979, p. 34)

A psychologist who had had experiences with LSD described ketamine as "experiments in voluntary death" (Leary, 1983, p. 375). Ramses Sputz noted:

One infrequent K [ketamine] user reports a classic near-death experience during his first trip. "I was convinced I was dead. I was floating above my body. I reviewed all of the events of my life and saw a lot of areas where I could have done better." (1989, p. 65)

Psychiatrist Stanislav Grof stated: "If you have a full-blown experience of ketamine, you can never believe there is death or that death can possibly influence who you are" (Stevens, 1989, p. 481-482). Anesthesiologist Barbara Collier reported that "ketamine allows some patients to reason that . . . the strange, unexpected intensity and
unfamiliar dimension of their experience means they must have died” (Collier, 1981, p. 552).

Attempts to explain NDEs as hallucinations are sometimes rejected by spiritualists because many persons insist upon the reality of their experiences (Osis and Haraldsson, 1977; Ring, 1980). However, 30 percent of normal subjects given ketamine were certain that they had not been dreaming or hallucinating, but that the events had really happened (Rumpf, Pedick, Teuteberg, Munchhoff, and Nolte, 1969; Siegel, 1978). The American Psychiatric Association defined a hallucination as “a sensory perception that has the compelling sense of reality of a true perception but that occurs without external stimulation . . . . Transient hallucinatory experiences may occur in people without mental disorder” (American Psychiatric Association, 1994, p. 767).

The apparently clear sensorium of some persons who have had NDEs has also been used to argue that the NDE is “real” and not a hallucination (Osis and Haraldsson, 1977; Ring, 1980). It is thus important to note that hallucinations in schizophrenia typically occur in clear consciousness and are perceived to be real (American Psychiatric Association, 1994). A personal conviction of the “reality” of an NDE does not invalidate scientific explanations. Some users of LSD have claimed that their minds were clearer than usual, and that the LSD world is real while the “normal” world is a veil of illusion (Grinspoon and Bakalar, 1979). Cardiac arrest survivors sometimes describe their resuscitation in detail (Sabom, 1982). Ketamine can permit sufficient sensory input to allow accounts of procedures during which the patient appeared wholly unconscious (Siegel, 1981).

One of the objections that has been raised against ketamine models of the NDE is that NDEs have been reported to be characterized by a sense of peace and well-being (Ring, 1980), while ketamine experiences are sometimes unpleasant, involving considerable anxiety. This objection arises largely from the manner in which data have been collected. For example, to investigate the NDE as Ring did requires that one have a pre-existing definition of what one is investigating. Such a definition will exclude many other mental phenomena that may be produced by the same neurochemical events as the NDE, just as ketamine produces a considerably wider range of phenomena than the NDE. It is reasonable to suppose that if all persons who had a cardiac arrest and were “unconscious” for a period were to be interviewed, many would not be able to report an altered state of any kind, just as many persons given ketamine can recall
nothing of the experience. There would then be varying percentages in both the cardiac arrest and ketamine groups who would report a range of phenomena, of which the NDE would be only one. Certainly a percentage of persons who have had cardiac arrests, for example, would report nightmares, anxiety, and panic.

Thus the argument that the neurochemical events induced by ketamine cannot explain "real" NDEs because ketamine also has other effects is weakened by the probability that factors precipitating "real" NDEs also have other psychological effects. As Rogo (1984) has pointed out, set and setting may go some way toward explaining the occasional incidence of anxiety reported in the ketamine literature. Anesthetists have reported that manipulations of set and setting can eliminate negative ketamine reactions (Cunningham and McKinney, 1983; Sklar, Zukin, and Reilly, 1981). It is also the case that ketamine's popular reputation for inducing nightmares is not well supported by the published scientific data; the "negative affect" is partly a myth. For example, the plastic surgeons Bruce Cunningham and Peter McKinney found "that many patients felt the hallucinatory phenomena to be pleasant and experienced no real concern or fear" (1983, p. 24). Garry Sklar, Stephen Zukin, and Thomas Reilly (1981) demonstrated that an informed patient who had good rapport with the anesthesiologist could experience the vivid imagery of full-dose ketamine without becoming frightened or alarmed. The marked increase in recreational use of ketamine (Stafford, 1992) is unlikely to have occurred were it to induce a large number of experiences characterized by negative affect.

Peter Stafford (1992) has described six broad categories of ketamine experience, and five of these can be related to near-death phenomena. This does not suggest that there is an endless heterogeneity of experience. A survey of both NDE and ketamine literatures does not support the argument that NDEs are more homogeneous and invariant than ketamine experiences.

Glutamate, NMDA and Sigma Receptors, and the Hippocampus

Most large neurons in the cerebral cortex use glutamate as their neurotransmitter. Glutamate, an excitatory amino acid, is central to the function of the hippocampus, a structure in the medial temporal lobe involved in memory and emotion and in integrating inputs from
many parts of the brain (Cotman, Monaghan, Ottersen, and Storm-Mathisien, 1987; Fagg and Foster, 1983; Greenamyre, Young, and Penney, 1984; Jansen, Faull, and Dragunow, 1989; Jansen, Faull, Dragunow, and Synnek, 1990; Monaghan, Bridges, and Cotman, 1989; White, Nadler, Hamburger, Cotman, and Cummins, 1977) and plays a vital role in all cognitive processes involving the cerebral cortex, including thinking, memory, and perception (Monaghan, Bridges, and Cotman, 1989; Oye, Paulsen, and Maurset, 1992; Squire and Zola-Morgan, 1988).

There is a binding site for ketamine and PCP, called the PCP receptor, attached to the NMDA receptor (Monaghan, Bridges, and Cotman, 1989). As they are part of the same entity, the two terms "PCP receptor" and "NMDA receptor" are sometimes used interchangeably. It was formerly believed that the sigma and PCP sites were the same entity, but it is now clear that sigma receptors have a unique distribution in the central nervous system and are not a form of opioid receptor (Jansen, Faull, Dragunow, and Leslie, 1991; Walker, Bowen, Walker, Matsumoto, De Costa, and Rice, 1990).

When the glutamate theory of the NDE was first proposed (Jansen, 1990b), it was not clear whether the hallucinogenic properties of ketamine were due to NMDA or sigma receptors. It is now known that these effects are due to NMDA receptor blockade (Krystal, Kasper, Seibyl, Freeman, Delaney, Bremner, Heninger, Bowers, and Charney, 1994), and that sigma receptors do not play an important role. Substances that bind to sigma receptors frequently have some affinity for NMDA and kappa opioid receptors at higher doses; but substances that bind to sigma receptors with a high degree of specificity, such as (+)pentazocine, do not produce NDEs at doses at which most of the binding is to sigma rather than NMDA and kappa opioid receptors (Muscacchio, Klein, and Canoll, 1990; Walker, Bowen, Walker, Matsumoto, DeCosta, and Rice, 1990).

Glutamate is excitatory. When present in excess, neurons die via a process called excitotoxicity. This is the mechanism of neuronal cell death in hypoxia/ischemia and epilepsy, conditions that have been proven to lead to excessive release of glutamate (Rothman, 1984; Rothman and Olney, 1986, 1987). Blockade of PCP receptors prevents cell death from excitotoxicity (Meldrum, 1987; Rothman, Thurston, Hauhart, Clark, and Solomon, 1987). This suggests that the brain may have a protective mechanism against the detected glutamate flood: a counter-flood of a substance that binds to the PCP receptor, preventing cell death. The brain is a well-protected organ with many
known defenses; it is reasonable to propose that it has protective mechanisms against excitotoxicity. This hypothetical defensive flood of substances to block the PCP receptors is the only speculation in the process outlined above; the other statements are strongly supported by experimental evidence (Ben-Ari, 1985; Benveniste, Drejer, Schousboe, and Diemer, 1984; Hoyer and Nitsch, 1989; King and Dingledine, 1986; Lobner and Lipton, 1990; Rothman, Thurston, Hauhart, Clark, and Solomon, 1987; Simon, Swan, Griffiths, and Meldrum, 1984; Westerberg, Monaghan, Cotman, and Wieloch, 1987). Endogenous substances have been found in the brain that bind to the PCP receptor, one of which is a peptide called alpha-endopsychosin (Quirion, DiMaggio, French, Contreras, Shiloach, Pert, Everist, Pert, and O'Donohue, 1984).

Explanations for the NDE

Some investigators have argued that the NDE must have a single explanation and then presented anecdotes to counter each of the scientific theories that have been proposed (for example, Ring, 1980) or have required that any scientific theory put forward must explain all of the experiences that have been labeled as NDEs (for example, Gabbard and Twemlow, 1989). It is more likely that the NDE is a final common expression of several different causes. Even then, the final "common" expression contains sufficient variability to suggest different types of NDE with different explanations. A multi-leveled interpretation is thus the most useful. The glutamate hypothesis of the NDE is not intended to apply to all NDEs, nor is it incompatible with many of the theories described below.

Psychological hypotheses

Depersonalization. The NDE may be an adaptive mechanism that alerts one to the threat of death while potentially overwhelming emotion is held at bay, allowing the reality to be integrated without panic (Greyson, 1983; Noyes and Kletti, 1976a, 1976b). This model is applicable when death is psychologically near, as in falling from a cliff. While protecting nerve cells from ischemic damage is then largely irrelevant, glutamate and NMDA receptors would certainly be in-
volved in producing the experience, as they play a key role in cognition and perception.

Regression in the Service of the Ego. Confronting death cuts off the external world, resulting in regression to a preverbal level of development experienced as mystical ineffability (Greyson, 1983). Loss of contact with the external world is one of the most characteristic effects of ketamine, and is probably due to blockade of NMDA receptors involved in sensory transmission. NMDA receptors play a central role in the transmission of incoming signals from all sensory modalities (Cline, Debski, and Constantine-Paton, 1987; Cotman, Monaghan, Ottersen, and Storm-Mathisen, 1987; Davies and Watkins, 1983; Greenamyre, Young, and Penney, 1984; Headley, West, and Roe, 1985; Kisvardy, Cowey, Smith, and Somogyi, 1989; Monaghan, Bridges, and Cotman, 1989; Oye, Paulsen, and Maurset, 1992).

State-Dependent Reactivation of Birth Memories. Movement through tunnels towards light may be a memory of being born, a "near-birth experience" (Grof and Halifax, 1977). NMDA receptor blockade could be the underlying mechanism for such a reactivation of primitive memories.

Sensory Deprivation. John Lilly (1978) explored ketamine as a means of inducing sensory deprivation, as a development of his work with sensory deprivation induced by flotation tanks. The observation that ketamine induces sensory deprivation was also explored by Barbara Collier (1972), who provided detailed accounts of NDEs induced by ketamine, including patients who claimed that they had died, separated from their bodies, and ascended to heaven.

How can sensory deprivation produce an altered state of consciousness? Memories may normally be suppressed by a mechanism that acts as a gate, admitting primarily external signals when we are fully conscious and concentrating on an external task (Siegel, 1980, 1981). If this input is dramatically reduced, for example, by ketamine or a heart attack, in combination with central stimulation, for example, by excessive glutamate release during hypoxia or epilepsy, stored perceptions are released and become "organized" into a meaningful experience by the mind (Greyson, 1983).

The hippocampus is the anatomical location of such a gate, and NMDA receptors form the molecular substrate of the gate. NMDA receptors have their highest concentration in the hippocampus, a part of the medial temporal lobe where data from the external world are integrated with internal programs. The NMDA receptor plays an important role in learning, and in the formation and retrieval of memo-
ries. The PCP receptor is referred to as a "gated channel" (Foster and Flagg, 1987). Whether the gate is open or closed depends on the degree of excitation, specifically, the position of a magnesium ion in the channel (Mayer, Westbrook, and Guthrie, 1984). Ketamine blocks this channel and closes the gate to incoming data (Collingridge, 1987; Cotman, Monaghan, and Ganong, 1988; McNaughton and Morris, 1987; Monaghan, Bridges, and Cotman, 1989; Morris, Anderson, Lynch, and Baudry, 1986).

The "white light" may result from central nervous system stimulation mimicking light on the retina, and a lowering of the phosphene perceptual threshold (Siegel, 1980, 1981). Sensory deprivation itself can produce profound alterations in consciousness (Lilly, 1961, 1978).

Drug-Induced Hallucinations

Administered drugs may explain some cases of NDEs, but in many no drugs were given with effects resembling the NDE (Sabom, 1982).

Temporal Lobe Epilepsy

Michael Persinger and Kate Makarec (1987) and Juan Saavedra-Aguilar and Juan Gómez-Jeria (1989) have reviewed evidence for the similarity between the phenomena experienced in temporal lobe epilepsy and NDEs. Glutamate is the key neurotransmitter in the temporal lobe, particularly in the hippocampus, and plays an important role in epilepsy. The neuropathology of epilepsy is believed to result from excitotoxic cell death (Ben-Ari, 1985; Cotman, Monaghan, and Ganong, 1988; King and Dingledine, 1986; Mody and Heinemann, 1987; Olney, Collins, and Sloviter, 1986; Sloviter, 1983).

It is possible that the postulated endogenous neuroprotective system becomes active in any excitotoxic situation, including temporal lobe epilepsy. The degree of excitotoxic cell damage, and the mental state, resulting from an incident in which there is a glutamate flood, whatever the cause, may depend on the final balance in each neuronal pathway between excitotoxic forces and neuroprotective mechanisms. This theory is supported by reports of persons who were oxygen deprived for prolonged periods, had a profound NDE, and survived the episode unimpaired (Sabom, 1982). The lack of apparent brain damage in these cases is hard to explain unless we postulate
that these may be persons with a particularly effective mechanism for glutamatergic blockade.

It is also possible that there is no protective mechanism, and that ketamine exerts its effects by mimicking some of the processes seen in temporal lobe epilepsy. Even though ketamine blocks glutamatergic transmission and prevents excitotoxic cell death, the effect of ketamine upon the human electroencephalograph (EEG) suggests that the final result of ketamine acting in the brain is the result of a complex interplay of forces. There is a reduction in alpha wave activity, while beta, delta, and theta wave activity are increased (Pichlmayr, Lips, and Kunkel, 1984; Schwartz, Virden, and Scott, 1974).

Ketamine has been reported to act both as an anticonvulsant (Celesia and Chen, 1974; Leccese, Marquis, Mattia, and Moreton, 1986; Mares, Lansitiaková, Vankova, Kubova, and Velísek, 1992; McCarthy, Chen, Kaump, and Ensor, 1965; Taberner, 1976) and as a convulsant (Bennet, Madsen, Jordan, and Wiser, 1973; Gourie, Cherian, and Shankar, 1983; Myslobodsky, Golovchinsky, and Mintz, 1981). M. S. Myslobodsky, V. Golovchinsky, and M. Mintz (1981) reported that ketamine could produce epileptiform EEG patterns in human limbic and thalamic regions, but that there was no evidence that this affected other cortical regions or that clinical seizures were likely to occur. This is quite consistent with the NDE model presented by Saavedra-Aguilar and Gómez-Jeria (1989) involving limited electrical abnormalities in the limbic system.

Thus the production of NDEs by ketamine is not necessarily at odds with the proposal that NDEs may result from abnormal electrical activity. David Reich and George Silvay concluded: "It is hard to draw objective conclusions regarding the anti-convulsant properties of ketamine . . . . Animal data are particularly difficult to interpret, because of inter-species variations" (1989, p. 188). Nevertheless, the weight of the evidence favors the conclusion that ketamine is probably anticonvulsant at the doses required to produce the NDE (Myslobodsky, Golovchinsky, and Mintz, 1981), favoring the hypothesis that an NMDA receptor blocker is released to produce the NDE.

Franz Vollenweider (1996) recently investigated the effects of ketamine using fluorodeoxyglucose-positron emission tomography (FDG-PET), a method that permits the imaging of metabolic activity in the brain. Subjects were given the drug and then had their altered states assessed using the Altered States of Consciousness Question-
naire, the Ego Pathology Inventory, and the inventory of the Association for Methodology and Documentation in Psychiatry. Imaging of brain activity indicated that “oceanic boundlessness” was strongly correlated with metabolic hyperactivity in the frontal cortex, “visionary restructurialization” was linked mainly to changes in the occipital cortex, and “dread of ego dissolution” was linked with changes in the thalamus and subcortical areas.

**Endorphin Release**

Daniel Carr (1981, 1989) proposed that NDEs resulted from a flood of endogenous opioids, or endorphins, as survival time was increased by giving opiate antagonists, such as naloxone, in fatal circumstances (Holaday and Faden, 1978). More recently, a sudden increment of beta-endorphin has been reported in the brain and body fluids of dogs who are “conscious” at the moment of death (Sotelo, Perez, Guevara, and Fernandez, 1995). The concept of a flood release of endogenous compounds is valuable, and it has now been established, as noted above, that a glutamate flood results in excitotoxic cell death in hypoxia/ischemia and epilepsy.

However, endorphins are not responsible for the NDE, as they are not potent hallucinogens (Oyama, Jin, Yamaga, Ling, and Guillemin, 1980). Injection of beta-endorphin into the cerebrospinal fluid has analgesic effects lasting well over 22 hours (Oyama, Jin, Yamaga, Ling, and Guillemin, 1980). This does not match the time course of a typical NDE, which is relatively brief.

Ketamine produces brief, deep analgesia (White, Way, and Trevor, 1982) due to NMDA or PCP receptor blockade (Parsons, Gibbens, Magnago, and Headley, 1988; Schoenberg and Sjolund, 1986). The limited psychotomimetic properties of some opioids, such as (-)pentazocine, result from binding to kappa opioid receptors, and to PCP receptors at higher doses (Musacchio, Klein, and Canoll, 1990; Pfieffer, Brantl, Jerz, and Emrich, 1986). However, the effects of (-)pentazocine binding to kappa receptors are described as feelings of cheerfulness and strength (Bellville and Forrest, 1968). The effects of selective and specific drug binding to kappa receptors do not match the profound alterations in consciousness produced by ketamine. With higher doses, more marked effects may appear as a result of binding to PCP receptors.
Claims that sigma-selective (+)isomers of benzomorphan opiates have psychotomimetic effects are not supported by the extensive literature based on research in humans, carried out in the 1960s, which demonstrated that it is the (−)isomers that have psychotomimetic properties, and those may prefer PCP receptors rather than sigma sites (Musacchio, Klein, and Canoll, 1990). The naloxone-reversible component is due to kappa opioid receptor binding, while the naloxone-insensitive component is due to PCP or NMDA receptor binding, not sigma binding (Walker, Bowen, Walker, Matsumoto, De Costa, and Rice, 1990). The role of opioid receptors in ketamine effects is controversial (Reich and Silvay, 1989). Naloxone could not reverse the effects of ketamine in humans (Amiot, Bouju, and Palacci, 1985), nor in dogs (Vaupel, 1983).

It is important to note that ketamine is supplied as a mixture of (+)ketamine and (−)ketamine isomers. Some of the controversy may be resolved by an improved understanding of the separate effects of the isomers and the doses at which they appear. As doses rise, the probability that drugs will bind to a wider range of receptors also rises. In this context, it is important to note that ketamine can induce NDEs at doses about four times less than those required for anesthesia (Grinspoon and Bakalar, 1979; Lilly, 1978; Sputz, 1989; Stafford, 1977).

Paul White, Jay Ham, Walter Way, and Anthony Trevor (1980) reported that it was (+)ketamine that has some opioid binding properties and that produced the most anesthesia, while (−)ketamine produced more “psychic emergence reactions,” or NDEs. White, Jurgen Schuttler, Audrey Schafer, Donald Stanski, Yukio Horai, and Trevor (1985) went on to show that (+)ketamine is about four times more potent as a hypnotic and analgesic, and has different effects upon the EEG than (−)ketamine, which may explain some of the confusion concerning whether ketamine is an anticonvulsant or a convulsant (Myslobodsky, Golovchinsky, and Mintz, 1981).

Saavedra-Aguilar and Gómez-Jeria (1989) have presented evidence from animal experiments that beta-endorphin may be epileptogenic (Henriksen, Bloom, McCoy, Ling, and Guillemin, 1978; McGinty, Kanamatsu, Obie, and Hong, 1986) to support their argument that beta-endorphin produces NDEs. While beta-endorphin may have these effects within the rat experimental paradigms used, it is common clinical experience that opioids do not induce epilepsy in humans (Meltzer, 1987). It seems more probable that released peptides would have protective functions rather than contributing further to excito-
toxicity. Saavedra-Aguilar and Gómez-Jeria (1989) also cited the finding of Tsung-Ping Su, Edythe London, and Jerome Jaffe (1988) that some steroids bind to sigma receptors, suggesting that steroids could play a role in NDEs. In fact, the steroid in question was progesterone, which is certainly not a hallucinogen, and S. Schwarz, P. Pohl, and G.-Z. Zhou (1989) have suggested that the affinity of progesterone for the sigma site is insufficient to result in significant receptor occupancy. It is possible that the endogenous ligand for the PCP channel is not a peptide but an ion or some other class of compound. Magnesium and zinc are involved in inhibiting the action of the NMDA receptor (Cotman, Monaghan, and Ganong, 1988; Thomson, 1986; Westbrook and Mayer, 1987).

Abnormalities in Blood Gases

Hypoxia. Richard Blacher (1980) suggested that hypoxia might give rise to the NDE. This proposal has been criticized by some authors (Sabom, 1982), because studies involving a slow fall in inspired oxygen produce mental clouding rather than NDEs (Henderson and Haggard, 1927). However, these studies are not an accurate model of events in, for example, cardiac arrest. Sudden hypoxia causes an excessive release of glutamate with resulting excitotoxicity, which can be prevented, as noted above, by ketamine.

Hypercapnia. A carbon-dioxide-enriched breathing mixture can result in typical near-death phenomena such as bodily detachment and the perception of being drawn towards a bright light. Diverse personality types produced similar reports, suggesting a shared neurological substrate (Meduna, 1950).

Serotonin

Like endorphins, serotonin effects may be contributory but do not play a central role in the NDE. Psychedelic drugs such as LSD are serotonergic in action, yet the psychedelic mental state is very different from the NDE. LSD frequently involves an overwhelming increase in sensory input from the external environment (Grinspoon and Bakalar, 1979), in sharp contrast to the cataleptic dissociation produced by ketamine. Psychedelic visual phenomena bear little relationship to the dreamlike images of ketamine and the NDE. The
“ego dissolution” experienced on LSD has a different quality from the conviction of having died that may arise with ketamine, and loss of contact with the external environment leading rapidly to the “tunnel experience” is not a typical psychedelic drug effect, although it may occur. Alexander Shulgin, a pioneer in the psychedelic movement, has argued that the dissociative anesthetics have little in common with psychedelic drugs (Shulgin and Shulgin, 1991).

Conclusion

The NDE is an important phenomenon that can safely be reproduced by ketamine, and the glutamate theory of the NDE can thus be investigated by experiment. Recent advances in neuroscience strongly suggest a common origin for ketamine experiences and the NDE in events occurring at glutamatergic synapses, mediated by the NMDA (PCP) receptor.

This theory represents an extension of previous hypotheses, and incorporates most of the neurobiological and psychological theories that have been put forward. It links many of these ideas, such as hypoxia, peptide release, temporal lobe epilepsy, regression in the service of the ego, reactivation of birth memories, and sensory deprivation, rather than being an alternative to them. Most of the planks on which this hypothesis is built are strongly supported by experimental evidence implicating glutamate and the NMDA receptor as unifying entities in the processes leading to an NDE. The main exception to this is the postulate that anti-excitotoxic agents can flood the brain, which remains to be clearly established.

References


Endogenous Ketamine-Like Compounds and the NDE: If So, So What?

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ABSTRACT: This commentary on Karl Jansen’s ketamine model for the near-death experience expands upon and raises additional questions about several issues and hypotheses: self-experimentation as a source of data; ketamine’s similarities to and differences from classical hallucinogens; the need for quantification of unusual subjective states; clinical research and toxicological implications of this model; drugs as gateways to “religious” states; and “evolutionary” versus “religious” significance of naturally occurring compounds released in the near-death state. I suggest future research that could help explicate several of these areas.

Karl Jansen’s paper cogently summarized the pre-clinical pharmacology of glutamate and N-methyl-D-aspartate (NMDA) receptors relative to the effects of ketamine, a dissociative anesthetic with “psychedelic” properties at subanesthetic doses. He also reviewed the less voluminous human literature on subjective effects of ketamine. He suggested that since ketamine, a “neuroprotective” NMDA receptor antagonist, elicits an alteration of consciousness with features similar to those described by individuals having a near-death experience (NDE), that an endogenous ketamine-like substance is released when an organism’s brain is faced with potentially life-threatening circumstances. The neuroprotective effects of such an endogenous NMDA antagonist thus are called upon by the organism to reduce the threat of brain damage. The NDE results from the psychoactive properties

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of these ketamine-like neuroprotective agents. Indeed, as is noted, "endopsychosins," with receptor binding profiles similar to ketamine, have been found in rodents.

The breadth of data and hypotheses presented by Jansen provides a springboard for discussing a wide variety of complex and intriguing issues. These include:

1) self-experimentation as a source of data;
2) ketamine versus "classical" hallucinogens, with respect to a cogent comparison of their subjective effects and the nature of their symptomatic overlap with the NDE, and with respect to their suitability for candidacy as an endogenous NDE-causing agent, or "NDE-ogen";
3) quantification of highly unusual mental states, including those elicited by NDEs and drugs;
4) clinical research and toxicology implications of the model;
5) the use of drugs as gateways to "religious" states; and
6) evolutionary/scientific or religious/vitalistic significance of endogenous NDE-ogens.

Self-Experimentation as a Source of Data

Jansen referred to the literature on human subjective responses to ketamine. He also drew upon his own NDEs and experiences with ketamine. He also suggested that his own experiences with the classical hallucinogens, that is, N,N-dimethyltryptamine (DMT) and lysergic acid diethylamide (LSD), demonstrate a lack of similarity between the effects of ketamine and these latter drugs.

Self-experimentation is a valuable and long-standing tradition in medical research, particularly with psychoactive materials (Szara, 1957). In this case, a discussion of the circumstances under which such experiences took place would strengthen Jansen's hypothesis. For example, why were these drugs administered, what doses were administered and by whom, and how many administrations? Were these double-blind studies? Was there an active placebo control for ketamine, especially one with a similar time course and dissociative properties (for example, nitrous oxide, carbon dioxide, short-acting parenterally-active tryptamines)? These all are important variables helping one assess the validity of experimental claims regarding psychoactive drug effects.
In the case of Jansen's NDEs, a fuller description also would shed light on the cogency of his comparisons of ketamine with the NDE. What happened to him? How close was he to death? What was the nature of the resuscitative interventions, if any? What did he see, think, and feel?

**Ketamine Versus “Classical” Hallucinogens**

*How Well Does Ketamine Replicate the NDE Relative to Classical Compounds?*

Jansen’s conclusion that ketamine “can reproduce all the features of the NDE,” while classical hallucinogens do not, was based upon comparing subjective effects of NDEs, ketamine, and classical compounds. This is an extraordinarily important point, and one that requires continued elaboration.

“Classical” hallucinogens include LSD, psilocybin, mescaline, and DMT. These drugs have been administered to thousands of patients and normal controls in clinical research, both psychopharmacologic and psychotherapeutic, over the last 50 years (mescaline for over 100 years).

While Jansen referred to previously published papers describing psychological effects of both ketamine and the NDE, his assertion that ketamine and NDEs are identical would have been strengthened by a more rigorous comparison, particularly regarding the nature of any differences between the two. Attention to differences might suggest gaps in theory, gaps that could be filled by additional hypothesis-driven experimentally-derived data.

Regarding differences, I have been struck by the fearful experiences many anesthetized patients describe as they are awakening from ketamine anesthesia, when blood levels compare to those attained with nonmedical or “recreational” use. These so-called “emergence phenomena,” while partaking of some of the particular perceptual and cognitive properties of the NDE, often are not pleasant nor desired to be repeated, and lack the equanimity and reinforcing effects that recreational ketamine users describe. Nor are they felt to be beneficial over the long run, that is, lessening fear of death and enhancing appreciation of life.

In addition, the highly addictive nature of the ketamine experience (for example, John Lilly’s injecting himself with ketamine every hour...
for weeks on end) does not comport with how one describes the consequences of the NDE. I am not aware of NDErs compulsively repeating the near-death state, for example, by frequent suicide attempts. Perhaps they become more risk-taking after an NDE, but this does not necessarily imply a desire to repeat the NDE as much as a lack of fear of death. On the other hand, it may be that increased risk-taking is an antecedent in those who compulsively use ketamine and other psychoactive drugs.

The lack of NDE-like properties of the classical psychedelics is not established. In fact, the research team at the Spring Grove State Hospital in Maryland used classical compounds such as LSD, psilocybin, and N,N-dipropyltryptamine (DPT) in their work with the terminally ill. This was because the overlap between descriptions of their volunteers' "peak" psychedelic experiences, mystical states, and NDEs seemed so pronounced (Pahnke, Kurland, Unger, Savage, and Grof, 1970).

Whenever effects of psychoactive drugs are described, one must pay careful attention to "set" and "setting," that is, expectations of the volunteer, and interpersonal and physical nature of the drug-taking environment. Along these lines, the intensification and distortion of environmental stimuli Jansen referred to as a hallmark of LSD effects, for example, could be powerfully altered simply by closing the eyes and lying still. Dissociation and dreamlike imagery, as described with ketamine use, very quickly develop in these circumstances.

Also important to consider is the effect of rapidity of onset of drug effects influencing interpretation of those effects. For example, the NDE-like nature of ketamine effects may have much to do with the rapidity of onset seen with intramuscular or intravenous administration. The absence of much time to prepare for (and defend against) effects, and the dissociative nature of these effects, may combine to be interpreted as death, or a deathlike state, since the sense of self is so heavily invested in the integrity of the body's constantly supplied perceptual input.

The classical hallucinogen with a similar temporal profile of activity is DMT. In our DMT studies at the University of New Mexico, the onset of intravenous DMT effects is nearly instantaneous, peak effects culminate at 1½ to 3 minutes, and are resolved by 20 to 30 minutes (Strassman, Qualls, Uhlenhuth, and Kellner, 1994). Several volunteers, none of whom had had a spontaneous NDE in the past, were convinced they had died as a result of the DMT injection, and
some even hallucinated resuscitation efforts being applied to their near lifeless bodies. Others viewed themselves lying in the hospital bed. Many said that they no longer feared death after having undergone a high dose of intravenous DMT. Many volunteers also met and interacted with “entities,” “angels,” “beings of light,” and “guides,” and “knew God” as a result of drug administration in our research setting. One volunteer, in response to an observing students’ comparing one of her seemingly bizarre dreams to the volunteer’s description of his just-completed DMT session, said, “What you are describing is a dream. This was different; this was real.” One volunteer even said, “People would all kill themselves if they knew how wonderful this place beyond everyday life is.”

Finally, I do not know of habitual repetitive use of DMT, as can occur with ketamine, despite the highly pleasurable effects of DMT. This is not due to tolerance developing to closely spaced DMT administrations, as we have demonstrated this does not occur (Strassman, Qualls, and Berg, in press).

Are There Classical Hallucinogen Candidates for an Endogenous NDE-ogen?

Jansen argued persuasively for a ketamine-like NMDA receptor antagonist as a naturally occurring NDE-ogen. However, it may be that other psychoactive compounds similarly affect brain function during dire physiological circumstances.

DMT, for example, is a naturally occurring hallucinogenic tryptamine, found in human blood, urine, and spinal fluid in many studies. Enzymes and precursors necessary for its production have been found in several species, including humans (Gillin, Kaplan, Stillman, and Wyatt, 1976). The “endopsychosins” with ketamine-like binding properties, on the other hand, have only been found in rodents, and there are few data concerning their existence since the initial 1984 paper describing them.

In summary, the subjective responses to, and longer-term effects of, the emergence phenomenon, recreational ketamine use, and NDEs, as well as ketamine addicts’ loss of control and consistently euphoric responses to the drug, are important data to consider when proposing a phenomenological identity of NDEs with ketamine inebriation. In addition, a broader interpretation of the classical hallucinogen human literature (Strassman, 1995), and consideration of
endogenous tryptamine psychedelics as naturally-occurring NDE-ogens, suggest that classical compounds provide a viable alternative or complement to a ketamine/NMDA-antagonist theory of NDEs.

Quantifying Unusual Mental States

As noted in the above discussion, there is a need for more finely tuned methods of comparing the nature of the subjective effects of ketamine, classical psychedelics, and the NDE. Comparison of subjective effects of drug-induced and nondrug-induced altered states of consciousness requires both careful clinical observation and interviews, in addition to some quantitative scoring of phenomena. Previous scales of subjective drug effects, such as the older LSD scales, predicated their questions and scoring methods on the assumption that psychedelics produced pathological states of mind—at least highly regressed, if not frankly psychotic. The standard scale, the Addiction Research Center Inventory (ARCI) compares novel drugs' effects to norms established for reference drugs, such as LSD, morphine, and benzedrine (Haertzen and Hickey, 1987). In generating normative data, the most popular LSD scales (Abramson, Jarvik, Kaufman, Kornetsky, Levine, and Wagner, 1955; Linton and Langs, 1962) and the ARCI used psychedelic-naive volunteers, who were told little if anything about what drug effects might be. In the case of the ARCI, abstinent narcotic addicts serving time in a penitentiary provided these data.

To remedy the problems both of assuming a priori the pathological nature of psychedelic effects, and of naive and/or psychopathic volunteers, we developed a new rating scale, the Hallucinogen Rating Scale (HRS), which may have relevance to the issues under discussion. The HRS was developed by interviewing healthy well-functioning hallucinogen users who found these drugs highly pleasurable and interesting, and the HRS was modified during our early work with intravenous DMT. While the development and initial data from the HRS are beyond the scope of this commentary (Strassman, Qualls, Uhlenhuth, and Kellner, 1994), how we clinically clustered questions is relevant.

We grouped the 120+ questions of the HRS by "clinical clusters," such as "perception," "cognition," "somatic effects," "volition," and "affect." These are "mental status examination" categories by which a clinical psychiatric examination takes place in any setting. This man-
ner of clustering items provided as good resolution of subtle dose effects as a purely statistical (principal components) analysis, and was superior to multiple biological variables in resolving dose effects. While the HRS is still in development, we do have preliminary data from an ongoing ketamine study in the United States suggesting that subanesthetic “psychedelic” doses of ketamine are remarkably similar to those of hallucinogenic doses of DMT. In addition, there are other preliminary data from a Canadian study showing that amphetamine does not produce the same type of psychedelic profile seen with DMT and ketamine.

Clinical Research and Toxicology Implications

It is often implicitly suggested, if not overtly stated, that NDEs are somehow good for you. The bliss, guidance, and reassurance by otherworldly beings, and grace-like features associated with the actual NDE; the beneficial changes in lifestyle or personal philosophy; improvement of mental health or substance abuse problems; and decreased fear of death all add up to sounding like a beneficial experience. The outcome sounds similar to that of a religious conversion, or a mystical state. Similar claims are well known from proponents of high dose hallucinogenic drug “psychedelic” psychotherapy.

While the model put forth by Jansen was primarily explanatory, it also might be used to support the use of ketamine to induce NDEs or NDE-like phenomena. These human studies could further elucidate the effects and mechanisms of action of ketamine, and explicate crucial similarities and differences among the subjective states induced by ketamine, classical hallucinogens, and NDEs.

Jansen’s suggestion that ketamine be given to those who have had a spontaneous NDE and a careful comparison made could be a pivotal study, and one that would benefit from the quantification of subjective states possible with the HRS. As well, DMT and/or other short-acting dissociative mind-altering agents, such as nitrous oxide and carbon dioxide, could be compared in the same volunteers. A simpler, useful, but less rigorous study, lacking the within-subjects design of the aforementioned one, would administer the HRS to those who have had a spontaneous NDE, and compare scores for their NDE with previously established norms for ketamine and other agents obtained from an independent sample.
Taken to its logical ends, this psychopharmacological approach may lead to experiments in which brains of immediately deceased individuals were assayed for endogenous NDE-ogens. The psychopharmacologists among us would want to blockade the effect of this NDE-ogen using selective antagonists, and then compare responses to nonpretreated immediately deceased! The ethical and technical issues boggle the mind.

More likely, however, is that studies could be undertaken with a therapeutic intent, where people in distress are treated with a ketamine-induced altered state. Such conditions might include drug abuse, posttraumatic stress disorder (PTSD), and the pain and suffering associated with terminal illness, ones often included in discussions of psychedelic-assisted psychotherapy. These are often intractable problems, frequently frustrating caregivers and family. There is great appeal to the concept of a magic bullet, one or several peak experiences such as an NDE or mystical/religious state that break through resistances and intractability, give a glimmer of hope and faith, and the conviction of a “higher reality.” Having glimpsed this new view, patients can now use it as a compass and reference point hereafter. Or, more specifically with regard to the terminally ill, if NDEs reduce fear of death, and ketamine produces an NDE, then perhaps a “dry run” using ketamine could ease this fear, and indeed, ease their real death.

The exclusively biologically-based clinician might at some point be able to point to clinical or preclinical data suggesting that these conditions—drug abuse, PTSD, fear of death—result from “excess glutaminergic tone.” The logical treatment would be an NMDA antagonist, such as ketamine. If the psychedelic effects were seen as an adverse side effect, agents that were effective antagonists and free of psychological effects might be developed, or the psychological effects selectively blockaded.

Before such therapeutic studies are undertaken, however, I believe that several issues should be thoroughly appreciated and inform any discussion preceding human therapeutic trials. The first three issues are common to well-conceived, hypothesis-driven clinical trials of new therapeutic agents; the fourth ventures into the murkier realms of pharmacological gateways to religious states.

The first issue concerns the basis for using ketamine as a therapeutic agent; that is, does it indeed reproduce an NDE? If careful human work demonstrates that it does, then a cogent rationale for applying an NDE to a clinical condition must be presented. If
ketamine does not reproduce an NDE, then its use as a treatment modality should not rely upon its similarities to an NDE. This is not to say there may not be psychotherapeutic uses of ketamine and other more typical hallucinogens, but that the bases for using them as experimental therapeutics must be clearly articulated.

A second issue is that of the risk:benefit ratio. If acute and longer-lasting adverse psychological reactions to ketamine occur, as they do with classical psychedelics (Strassman, 1984), it would be important to plan for this contingency. This is particularly germane if terminally ill patients were studied, and little time remained to remedy the consequences of a frightening ketamine-induced near-death state.

Third, ketamine has been reported to be neurotoxic in certain animal models (Olney, Labruyere, and Price, 1989), its toxicity reversed by diazepam (Olney, Labruyere, Wang, Wozniak, Price, and Sesma, 1991). Since diazepam also prevents the "psychotomimetic" emergence phenomena seen in humans, it is possible that the NDE-like symptoms of ketamine are secondary to neurotoxicity. This also suggests that development of ketamine-analogues with psychedelic effects but lacking neurotoxicity will be difficult.

**Drugs as Gateways to Religious States**

The final issue I would like to raise is that of "set" and "setting" for the use of ketamine. This begins to touch upon the more troubling and controversial relationship between drugs and religious experience, a topic that continues to stir rancorous debate. There is even now interest in renaming these drugs "entheogens," generating the divine/God within. In my own case, religious claims for these drugs contributed to my interest in studying these drugs in a clinical research setting. Part of this debate addresses the question whether hallucinogens, including ketamine, are inherently "good" drugs for people to take because they provide actual paths to personal growth, either religious or psychological.

These issues should be appreciated in designing practical elements of hallucinogen administration to humans, particularly therapeutic trials. Who should be given ketamine, and how? Who should give ketamine, and how? Should administering clinicians have their own experience with the drug? Do they need a background in religion and philosophy to hold empathically, support, and nourish the experience of their patients? Do the conditions elicited by ketamine and
other psychedelics properly belong within the purview of psychiatric clinicians and research scientists?

What do we do with the “religious” utterances of our patients? For if these drugs do elicit states best described in religious and spiritual terms, does the administering clinician essentially dash these beliefs by understanding and interpreting them as purely biochemical perturbations with subjective counterparts, never mind intimations of immortality and divine revelation, no matter how powerfully held by the experimenter these latter beliefs are? Is there something pharmaco-logically useful in the chemical nature of these drugs, that by their revelatory properties could substitute for or enhance years of long self-analysis and discipline? Should we tell patients that?

Our research team was alert to these factors while working with DMT. While our studies were not explicitly therapeutic in intent, part of my interest in performing this research was to assess the impact of a “neutral” set and setting on a psychedelic drug-induced extreme alteration in consciousness. I wanted to see if DMT was “good,” “bad,” or “indifferent” in its “nature.”

My conclusion after administering more than 400 doses of DMT to over 50 relatively healthy, experienced hallucinogen-using volunteers, is that there is nothing inherent about the drugs that has a beneficial effect. Neither are they pharmaco-logically in and of themselves dangerous. The nature of, and sequelae to, the experience are determined by a complex interplay of the drug’s pharmacology, the nature (states and traits) of the volunteer at the time of drug administration, and the nature of the relationship between the individual and his or her physical and psychological environment.

The volunteers who benefitted most from their DMT sessions were those who probably would have gotten the most out of any “trip,” drug or otherwise. Those who benefitted least were those who were the most novelty-sated and less likely to incorporate new concepts, perceptions, or feelings, the novelty being more important than what was novel. And the most difficult sessions took place in various degrees of contributions of two factors. These were, first, an inability voluntarily to give up the internal dialogue and body-awareness; and second, ambiguous relationships between the volunteer and those in the room at the time (usually guests or students introduced to the volunteer right before drug administration). Thus, the “religious,” “adverse,” or “banal” effects resulting from drug use depended more upon the volunteers and what they and those in the room brought
to the session, than from any indwelling characteristic of the substance itself.

For example, two people we studied had minimal responses to a high dose of intravenous DMT (I do not know if there are cases of lack of response to ketamine, too). One of these volunteers was a highly experienced meditator, while the other was a bartender who preferred sailing. The first volunteer had a meditation-induced religious experience some years before, and my facile explanation was that his "enlightenment" experience might have changed his neurophysiology in such a way as to raise his threshold radically for drug-induced mystical states. However, I am more at a loss explaining the lack of response in the other volunteer. We joked with him that he was already enlightened but just didn't know it!

There are clinical research implications of these issues, which will affect experimental designs and the nature of the outcome data. If acute drug-induced alterations in consciousness are to be used in a traditional clinical research setting, and therapeutic intent is explicit, I believe the issue is not whether or not a psychedelic drug by itself is useful: it is not. Neither is the issue whether or not "NDEs," drug-induced or spontaneous, are therapeutic. The issue is rather whether a drug affects psychological processes, and if so, how such effects can be turned to enhance the therapeutic process. And, if these subjective effects are best conceptualized in "religious" terms, is it necessary to incorporate pastoral counseling and/or 12-Step or other "spiritual" modalities and explanatory models into the design of any study?

In summary, therefore, an appropriate research model might treat patients in an accepted manner, and compare results when a psychedelic drug or appropriate placebo is added. The interaction of drug, psychology, biology, and social environment could all be assessed carefully. This design would clarify the nature of the drug interactions with the particular clinical condition and its treatment in a particular setting. For example, is there a relationship between ketamine's effects on motivation or insight, and abstinence from cocaine use or frequency of flashbacks in PTSD?

Scientific/Evolutionary or Religious/Vitalistic Significance of Endogenous NDE-ogens

This is the most speculative, but among the most compelling, area raised by any biological model of the NDE. That is, "If so, so what?"
Why would nature design biology in this way? Is it a coincidence, or is it "for a reason"?

Jansen did not include religion and philosophy as branches of inquiry within which the NDE might be advantageously studied. The suggestion that NDEs actually are early stages in the movement of the life force into a noncorporeal state or "afterlife" has been an issue well discussed by major religions; and the possible existence of consciousness existing "outside" the human body is of intense interest to mind/brain scientists and philosophers. However, Jansen also referred to "religious experiences that sometimes result" from psychedelic drug use. In describing his own ketamine experiences, he described “emergence into the light” (not a light, but the light), and encountering “'God'” (his quotes).

This apparent ambivalence may reflect the general discomfort “mechanistic,” "areligious,” “objective” scientists feel when carefully examining subjective reports of NDEs, psychedelic drugs, and similar states. For while there are well-documented biological correlates and perhaps precursors of religious, NDE, and psychedelic states, the function, nature, and origin of these perceptions is not adequately addressed by a rigidly biological perspective. This is not because of any “antiscientific” axe to grind, but solely because those who describe these states, even those like Jansen who claim they are “non-religious,” routinely do so in religious and spiritual, rather than biological or adaptational, terms. And, the adaptive or biological significance of an endogenous NDE-ogen is difficult to discern.

Perhaps it is the nonmaterial nature of these phenomena that is so vexing to the materially-minded neuroscientist. For example, understanding how the television set works does not yield any information regarding from where the images and sounds arise. Nonmaterial subjective (and by its nature, wholly private) experience includes dreams, psychedelic and religious states, and NDEs. How do we approach the scientific study of phenomena that we cannot now measure with mechanical instruments, but can only verify with our subjective experience?

In these states, the body “drops away,” as it were, but an ongoing, undeniable, compelling reality continues to be experienced. Brain metabolism continues, but what is being observed, and why is it no less “real” than objective, instrument-measurable, externally verifiable, consensually validated experience? Ketamine or “endopsychosin” effects on NMDA receptor function at discrete, strategic brain sites could be invoked, but this reductionism can become absurd. For ex-
ample, is "everyday reality" as "real" and compelling as it is because of NMDA receptor function? Perhaps it is the case that the NMDA receptor is blockaded when the organism is perceiving a nonmaterial world!

Different versions of what constitutes "science" might lead to means of proceeding with the "scientific" study of "religious" phenomena. For example, Jansen stated that "within a scientific paradigm, it is not possible that the 'spirit rises out of the body . . . .' " Has this been disproved? Who has looked? And with what tools?

Jansen suggested that "the reproduction of NDEs by ketamine is unlikely to be a coincidence." This is because NMDA antagonists such as ketamine are neuroprotective, and have NDE-ogenic "side effects." From a "scientific" point of view, however, it is difficult to suggest that it is anything other than a coincidence. A coincidence is a correspondence of identity in space occupied or temporal position, or a remarkable occurrence of events at the same time or in the same way. If there is to be the maintenance of scientific credulity, the similarities of ketamine and other psychedelics to the NDE must be a coincidence. How could they be otherwise?

If the NDE-ogenic properties of endogenous neuroprotective agents are not a coincidence, the existence of these similarities would support one of two possible hypotheses. The first hypothesis would be that this association confers an evolutionary advantage on the organism or species. However, why would not a neuroprotective agent produce sensory and cognitive dulling, inhibition, and sedation, blurring the transition to unconsciousness and death? What is the adaptational or competitive advantage of an individual's near-death state being a psychedelic or revelatory experience, of an otherworldly nature?

The second hypothesis is that the association supports a "nonverifiable" explanation (at least at this point in our scientific maturity); that is, that NDEs and ketamine/psychedelics establish the existence of nonmaterial realms.

Jansen rejected this latter hypothesis, and instead asserted that since ketamine-like compounds are released at death, these compounds (by no coincidence) produce NDE-like mental changes. There is, however, implicit in this, the assumption of a purposive (and not mechanical) cause directed to a definite end. That is, it is an explanation of nature in terms of utility or purpose. This is vitalism, or teleology, a distinctly religious or spiritual school of thought.
The most cogent purposive reason for this association is that this indeed is an accurate preview of what happens at the time of death: a rapid transition to a nonmaterial realm, free-standing, autonomous, peopled by familiar and unfamiliar inhabitants. One may be forced to conclude that this is what does happen if it is not a coincidence. Freed of the somatic feedback, the conscious life force moves towards a nonmaterial realm, completely convinced of its veracity, and since there is no body, and therefore no ego (that is, no body-ego), this is the conscious moment inhabited by the mind.

If this were the case, then the release of ketamine-like or other endogenous psychedelics would be the brain’s correlate of awareness leaving the body, rather than the cause of it “feeling that way.” This would be similar to the fact that functional brain imaging techniques demonstrate identical findings regardless of whether perceptions are based upon external stimuli or upon imagined stimuli (Le Bihan, Turner, Zeffiro, Cuénod, Jezzard, and Bonnerot, 1993). They reflect correlates or mediators of perception, rather than attesting to the “reality” of what is perceived.

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Is the Near-Death Experience Only N-Methyl-D-Aspartate Blocking?

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ABSTRACT: Karl Jansen's interesting hypothesis that near-death experiences (NDEs) result from blockade of the N-methyl-D-aspartate receptor has several weaknesses. Some NDEs occur to individuals who are neither near death nor experiencing any event likely to upset cerebral physiology as Jansen proposed; thus his hypothesis applies only to a subset of NDEs that occur in catastrophic circumstances. For that subset, the clarity of NDEs and the clear memory for the experience afterward are inconsistent with compromised cerebral function. Jansen's analogy between NDEs and ketamine-induced hallucinations is weakened by the fact that most ketamine users do not believe the events they perceived really happened. Temporal lobe seizures do not resemble NDEs as Jansen postulated; they are confusional, rarely ecstatic, and never clear, as are NDEs, nor are they remembered afterward. Jansen's hypothesis assumes the standard scientific view that brain processes are entirely responsible for subjective experience; however, NDEs suggest that that concept of the mind may be too limited, and that in fact personal experience may continue beyond death of the brain.

Karl L. R. Jansen has proposed a hypothesis describing a mechanism that makes a major contribution to the understanding of the near-death experience (NDE). He suggested that the NDE is the result of the blocking of the phencyclidine (PCP) site on the N-methyl-D-aspartate (NMDA) receptor. This is an interesting hypothesis, and it is likely that the suggestion that the NMDA receptor is involved in a subset of NDEs is correct. However, Jansen's paper, like many before it, suffers from a number of weaknesses, some outlined by the

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author. In reviewing this hypothesis, it is important to look at its implications from several different levels. When arguing for an explanation of the NDE, chemical, clinical, and philosophical aspects should all be included. I shall discuss these areas independently.

Jansen started his paper with a philosophical statement concerning death and the nature of mind. This point requires answering, but for the first part of this article I would like to take the position, suggested by Jansen, that mind arises from neuronal activity, and that consciousness is local to brain processes.

The first point is: how do we define an NDE? Are we to consider only those NDEs that occur with catastrophic brain failure, or should we include those NDEs that occur in different circumstances? Jansen did not suggest that his theory is applicable to all cases of NDEs, but argued that it can explain most experiences, put generally, because the PCP receptor is involved in perception.

The full breadth of near-death phenomena came to my attention after a television program and publication of several articles in the United Kingdom. The British branch of the International Association for Near-Death Studies (IANDS-UK) and I have received more than 2,000 letters containing experiences. From these letters we selected a subset of experiences that we felt were most typical of the core NDE. We mailed 500 questionnaires to this group of people and received over 370 replies (Fenwick and Fenwick, 1995). The selection of this data set was biased by several important factors. First, the group was self-selected. Second, the people who wrote were those who were sufficiently interested in their experiences to want to communicate something that was important to them. This adds a significant selection bias, in that people who have had negative or neutral experiences are much less likely to want to communicate them than those who have had positive experiences. However, accepting these deficiencies, these NDEs were reported as having occurred under many different situations, some of which were not near death, nor accompanied by any threatening event likely to have upset cerebral physiology in the way proposed by Jansen's hypothesis.

Experiences were reported to have occurred when experiencers were awake and relaxed, when they were depressed, and in minor infections and in routine anesthesia. We rejected those that were reported to have occurred in sleep. The largest number certainly occurred in catastrophic circumstances. Our sample makes the point that NDEs judged entirely by their phenomenology occur in many different circumstances; thus any theory that links the NDE only to
brain catastrophe or to a special brain physiological mechanism must provide only a partial and limited explanation. Elizabeth Fenwick and I (Fenwick and Fenwick, 1995) have suggested that a detailed look at the phenomenology of the NDE allocates it to a group of experiences that is already well studied and understood, that of the mystical experience. This explanation has the advantage that mystical experiences too have multiple causes. The hypothesis put forward by Jansen should thus be limited to a subset of NDEs that occur in catastrophic circumstances.

Jansen argued, correctly in my view, that a clear sensorium and a feeling of absolute reality do not negate the suggestion that these experiences are hallucinations. From a scientific point of view it is clear that the majority of the NDEs must be hallucination, if one excludes those out-of-body experiences for which a veridical nature is claimed, as the world described is private to the individual and not held in common between subjects. The fact that we define the NDE mainly as an hallucination is of little help in terms either of the experience's likely genesis or of its philosophical explanation. It simply raises questions about the subjective nature of mind. It does, however, help to direct attention, as Jansen has done, to other situations in which hallucinations that have a similar form occur.

I was interested in the comment that only 30 percent of normal subjects given ketamine were certain that the events had really occurred. In NDEs this percentage is much higher, and this point weakens a ketamine-like effect as the only explanation. However, in defense of the ketamine hypothesis, it could be that those people given ketamine would naturally tend to attribute whatever experience they had to the drug, and so would be less likely to regard it as "real."

The phenomenon of a clear sensorium in catastrophic brain states is more difficult to explain. Any physician dealing with head injury, epilepsy, or altered cerebral physiology knows that as cerebral function becomes compromised it becomes disorganized. Even in such simple circumstances as ordinary fainting, recovery from the faint is recovery from a confusional process. Acute cerebral catastrophes result in confusion and not clarity. This important fact is overlooked by those attributing simple chemical explanations to the NDE. Although ketamine may produce experiences that are similar to the NDE, and Jansen has argued cogently that it does, he does not explain how these same experiences can arise in a dysfunctional brain. His argument is that when brain processes have been so disorganized
that there is loss of consciousness, consciousness can then be resynthesized in its clarity by a brain mechanism such as flooding the brain with NMDA inhibition. Surely the very fact that consciousness has been lost would argue that cortical activity is insufficient to sustain high quality and clear consciousness as would be required for an NDE.

The only way round this dilemma is to argue that the experience arises as consciousness is being recovered or lost, when cerebral function is still sufficiently intact to maintain coherent and clear cerebral experience. There are arguments, mainly related to memory, that I will discuss further below, which make it unlikely that many NDEs could occur as consciousness is being lost. The alternative conclusion would therefore have to be that NDEs occur with the return of the cerebral processing involved in ordinary conscious experience. However, the difficulty here is that recovery from a cerebral catastrophe is via a confusional state and it thus seems unlikely that an arousal through confusion could produce both the clarity of the experience and the confusion of arousal.

In our series there were some specific accounts that made this point even more starkly. We had patients who were head-injured and whose arousal was confusional and showed all the characteristics and mental states that would be expected after a severe head injury. Yet within this dense confusional state, but attributed by the individual to the time of unconsciousness, was full memory of a wonderfully clear NDE. It is worth noting that in severe head injury memory for the accident and for the confusional awakening in hospital is absent, and this was so in our cases of head injury. Except by special pleading, it is not possible with our current understanding of cerebral functioning to explain, on a simple chemical theory, how, within dense unconsciousness and with absence of memory, the brain can structure and remember a clear comprehensive experience. This is an interesting point and is a challenge to our current understanding of brain function (Cartlidge, 1991; Teasdale, 1991).

One of the most puzzling features of NDEs, besides their clarity in the presence of cerebral catastrophe, is the clear memory for the experience. As mentioned above, memory is very sensitive to brain injury, and length of amnesia before and after unconsciousness is a way of determining the severity of the injury. It is thus unlikely that cerebral events occurring during this period of total amnesia would ordinarily be remembered (Cartlidge, 1991; Teasdale 1991).
Jansen described the excitatory and inhibitory properties of ketamine and decided on balance against it being excitatory, though it is probably neuroprotective. He concluded that it is likely to be inhibitory. This leads to a discussion of the role of epilepsy in NDEs. There is much about the possible role of epilepsy, abnormal temporal lobe functioning, and abnormal hippocampal functioning in the NDE literature (Saavedra-Aguilar and Gómez-Jeria, 1989), which Jansen, quite rightly, wanted to include in his theory. In my view much of the discussion of temporal lobe epileptic (TLE) activity as a component of the NDE argues without the data to support it.

Let's start with temporal lobe seizures. We can divide these into those starting in the lateral temporal cortex and those arising from the hippocampus or the amygdala, the medial temporal structures. Let’s consider those arising from the hippocampus or the amygdala. The international definition of these seizures is partial complex seizures; they are termed “complex” because they lead to an alteration of consciousness. This alteration in consciousness is confusional. When patients have seizures originating in the medial temporal structures they usually have a disorder of consciousness, and the mental phenomena are usually those of fear or extreme fear.

Positive auras and feelings, so common in the NDE, are reported in only a very small minority of medial temporal seizures. In William Gowers’ (1881) study of 505 epileptic auras only 3 percent were said to be emotional and none positive. In William Lennox’s (1960) study of 1,017 auras, only 9 were said to be pleasant (0.9 percent), and of these “only a few showed positive pleasure.” Wilder Penfield and Kristian Kristiansen (1951) cited only one case with an aura of a pleasant sensation and it was followed by an epigastric feeling of discomfort. Until 1980, no cases of temporal lobe epilepsy and an ecstatic aura had been reported (Cirignotta, Todesco, and Lugaresi, 1980). Despite this, ecstatic states were frequently attributed in the literature to TLE. As Henri Gastaut (1978) explained, this was because people expected ecstatic states to be present (Fenwick, 1983).

Thus the phenomenology of discharges in this brain area bears no resemblance to that of the NDE. More importantly, when the seizures spread out from the medial temporal structures into the temporal cortex more complex phenomena may arise, but these are always confusional and never complex and clear like the NDE. It is thus unlikely that any alterations in electrical activity of a seizure type arising in the medial temporal structures could contribute to the NDE.
Those seizures arising from the lateral temporal cortex do contain more complex phenomena. There may be alterations in space and time and body image. Déjà vu experiences can also arise, suggesting the false attribution of meaning to current experiences. But again these seizures are partial complex seizures and confusional. Thus abnormal discharges in the temporal lobe may produce confusional fragments of phenomena sometimes seen in NDEs (Williamson, Wieser, and Delgado-Escueta, 1987). This is a very long way from arguing that seizure discharges in these areas, resulting from brain catastrophe, can give rise to the clearly remembered, highly structured NDE. Finally, seizure discharges that involve or spread into the medial temporal structures lead to abolition of memory for what occurred during the seizure, and afterwards in the automatism, if one occurs. Many patients with prolonged automatisms have no memory for the complex events that occur during their wanderings. Thus even if temporal lobe seizures did contribute to the NDE the experiences would not be remembered. As yet I do not think there is sufficient evidence to support the idea of seizure discharges in the temporal lobe being responsible for the NDE.

Quite clearly, drug experiences, which mobilize widely different brain areas in addition to the temporal lobe, can produce higher order experiences that also include some of these same fragments of temporal lobe experience seen in temporal lobe seizure discharges. This is, however, not to argue that temporal lobe seizure discharges lead in any sense to these wider coherent experiences. It must also be recognized that epilepsy surgery units involved in temporal lobe surgery routinely implant indwelling cerebral electrodes either into the hippocampus and amygdala or beside the hippocampus and amygdala (foramen ovale electrodes); these electrodes usually show continuous or frequently abnormal electrical activity. Epileptic spike discharges are common. Yet none of these discharges are correlated with NDE-like phenomena. Indeed, unless the individual epileptic discharges spread to form either local or more general seizure discharges, there is little effect on cognition, and the individual is unaware that they are occurring (Ojemann and Engel, 1987). Thus on both electrical grounds and clinical grounds, the argument that temporal lobe seizure-like activity is responsible for near-death phenomena must be discarded. There is one caveat: all the data so far described refer to patients with epilepsy and taking anticonvulsant drugs, so we do not know how the nonepileptic brain would respond, though it is unlikely to be very different.
If one is to retain the idea of a change in hippocampal or hippocampal-amygdalal function during the NDE, one must argue specifically for very organized changes in functioning. Much more is now known about the function of the hippocampus. First, postmortem specimens resected from patients with temporal lobe epilepsy usually show the presence of bilateral hippocampal disease and hippocampal cell loss (Babb and Brown, 1987). It is thus possible to have major pathology within the hippocampus and for none of these experiences to arise. Clearly the demonstration of pathology does not necessarily negate the possibility that these structures mediate the NDE, but it does suggest that damage to these structures does not necessarily lead to an NDE, as was postulated in Jansen's article.

Further, there is now a large body of data showing the relationship between hippocampal damage and memory function. It seems likely that in right-handed people the left hippocampus is involved in verbal memory and the right hippocampus in visuospatial memory (Jones-Gotman, 1987). Damage to one hippocampus early in life may result in the other hippocampus taking over, to some extent, the function of the damaged side. Clearly, arguing that electrical discharges in the hippocampus give rise to the full panoply of phenomenology of the NDE is far too simplistic. However, something can be salvaged from the hippocampal theory. If it is postulated that the hippocampus is involved in the direct way Jansen suggested, then an interesting hypothesis can be generated as to the content of the memories that occur in the NDE. If one hippocampus is damaged, there should be an appropriate lack of recalled memories in the NDE, either visuospatial or verbal, depending on the side of the damage.

Turning now to the nature of mind, Jansen quoted the standard identity theory, which states that brain processes are entirely responsible for, and identical with, subjective experience. In other words, he presented the standard scientific view (Dennett, 1993). However, one of the interesting and exciting points about the NDE is that it suggests that our view of mind may be too limited. It raises the possibility that mind may be nonlocal. Nonlocal means that although brain processes within the skull are involved in the structuring of mind, the effects of mind may extend beyond the brain. If nonlocality is a possibility, we have then to ask what we mean by “mind.”

For simplicity's sake I will define mind as “subjective experience,” although I am aware of the limitation of this definition and the philosophical problems that arise by using it. Many scientifically valid parapsychological experiments have suggested that subjective expe-
perience may be transmitted from brain to brain directly in telepathy, or influence physical matter outside the brain in psychokinesis (Bem and Honorton, 1994; Jahn and Dunne, 1987; Wolman, 1977). These data are not well known in scientific circles and are seldom quoted in scientific articles when subjective experience and brain function are discussed. The reason for this is that as yet we have no clear theory to explain paranormal experiences, and as such these phenomena are outside science. One of the challenges of the NDE is that it puts before us phenomena that could be explained much more easily by such a nonlocal theory of mind than by standard scientific thinking.

Out-of-body experiences are frequently reported to occur in the early part of the NDE. These out-of-body experiences have a heterogeneous phenomenology and some can be explained quite easily by conventional science, which suggests that the brain creates our subjective experience of our body and its position in space from sensory information. The body is experienced as being elsewhere, for example on the ceiling, either for psychological reasons or because an alteration in brain physiology, such as may occur in acute anxiety, transforms the coordinates of the body's position in subjective space. What the subject thinks and hears while apparently on the ceiling is simply the continuation of sensory flow into the brain allowing an altered construction of reality.

However, anecdotal cases have been reported that seem to indicate quite persuasively the involvement of some other mechanism and the occurrence of veridical out-of-body perceptions. The subject apparently experiences objects in the external world that could not be perceived by the senses. An example is the out-of-body experience during an NDE, when the subject may feel that he or she floats into a different room and hears a conversation that could not possibly have been heard otherwise. In this case, if the account is correct, data have to have been received directly by the mind/brain without intervention of the senses. There are numerous anecdotal accounts in the near-death literature of this kind of experience. It would be interesting to know if there are similar accounts by people who have had out-of-body experiences under ketamine, and if so, if there is any objective evidence that they are veridical.

Other newer, nonparapsychological theories have sought to explain nonlocality of mind by suggesting that quantum mechanical processes may take place in the brain. Stewart Hameroff (1987) and Roger Penrose (1994) argued for special energetic processes either in
the cell (microtubules) or on the cell membrane (Frohlich oscillators or Bose-Einsten condensates) that would allow quantum mechanical effects to occur in the brain. Prior to these theories the brain had always been thought to be "too hot and too wet" for quantum mechanics to play a part in the way it operates. These are exciting new theories, as they would support the idea of nonlocality of mind.

Finally, although this was not the thrust of Jansen's article, it is worth a look at the philosophical statements at the beginning of his paper. There was an assumption that chemical and brain processes are all there is to mind; understand brain processes and mind is completely explained. Some of the phenomena of the NDE suggest that subjective experience may be maintained in the face of severe cerebral catastrophe. If this is a possibility, then the maintenance of subjective experience when brain function is severely disorganized has consequences for our understanding of brain processes and the nature of mind. It even raises the possibility that there might be a continuation of subjective experience after brain death.

This is an area of growing interest in philosophy. Our implicit everyday scientific assumptions in science do require questioning. Current science is based on the philosophical assumptions of Galileo, who argued for a two-stuff universe, matter and energy, and for this stuff to have primary and secondary qualities. Primary qualities are the objective qualities of the physical world, such as weight, velocity, and momentum. Secondary qualities are the qualities of subjective experience, such as smell, taste, love, and beauty. Galileo argued that secondary qualities were not in the domain of science; thus our current scientific theories are all based on an objective external world that contains no secondary qualities. And yet we insist on using these theories to try to explain these very qualities, which by definition cannot be explained by Galilean science.

More recently, Thomas Kuhn (1970) pointed out that what we think of as independent objective scientific facts are "value laden." By this he meant that scientific facts arise within a theory that itself is part of a culture, and thus our particular view is cultural, and so our objective facts are relative. Max Velmans (1991, 1993) maintained that an objective fact is a subjective cognition held in common between a group of people and verifiable by them, whereas a subjective cognition is private to the individual, does not have the quality of objective validation, but is no less true. With these limitations, it is clear that our science as currently formulated is not able to explain the implications of the NDE. Science is able to note brain correlates
of the NDE where they exist, but it cannot argue from these corre-
lates to the significance, or even the presence, of subjective experi-
ence. One is left only with the subjective accounts. Science, by
definition, cannot explain subjective experience, so it can neither re-
fute nor confirm the possibility that these subjective accounts do in-
deed suggest that some form of personal experience may continue
during the unconsciousness of brain catastrophe or even after brain
death.

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Which Comes First: Consciousness or Aspartate Receptors?

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ABSTRACT: This paper is a critique of Karl Jansen's hypothesis that near-death and ketamine experiences are caused by blockade of N-methyl-D-aspartate receptors. An assumption that consciousness and its alterations are merely the product of neuronal activity is only one of many possible beliefs about reality. An alternative, which can be verified through one's own direct experience, is that consciousness is always a subject and body is only its object. The objects come and go; consciousness remains.

Near-death studies is a field where different disciplines must necessarily cooperate. The relevant disciplines here include not only medicine and neurosciences but also religion, philosophy, and transpersonal psychology. In this context, attempts to reduce an explanation of the near-death experience (NDE) to mere interactions of neuroreceptors look especially archaic. Karl Jansen's article is certainly an example of such biological reductionism.

Jansen's article began with the assertion on simple logical grounds that NDEs are not evidence for life after death: death is defined as the final irreversible end. Now who is the authority to define death as the final end? It happens to be the Oxford English Dictionary! Jansen quoted it to support his assertion, tacitly assuming that the reader has the same faith in the final authority of the Oxford English Dictionary.

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Dictionary as he does. On a planet where billions of people believe in reincarnation or some form of life after death, the Oxford English Dictionary holds the authority in such questions as death for rather a minority. This should be taken into consideration when “simple logical grounds” need to be established.

But since Jansen's paper is a scientific one, let us put beliefs and faiths aside, and address the experience. For whom is death “the final end”? It is the external observer only who witnesses the “final cessation of vital functions” of the body, but what is the inner experience of the one whose body becomes a corpse? The main problem with the “objectively scientific” study of consciousness is that it always overlooks the simple experiential fact that consciousness cannot be objectified. In other words, consciousness is always a subject, and never an object. It is only when consciousness is mixed with an object, such as the body, that the confusion arises.

Even in common language we say “my body.” We don't say “I-body” or “me-body.” Everyone can see through his or her own direct experience that one is aware of one's body. In other words, the body is the object of one's awareness. This is a simple experiential fact. Now, when the physical body ceases to be the object of one's awareness, this awareness simply continues to be conscious of other objects, and that's what happens in death, in the NDE, in the ketamine experience, and in deep meditation. Basically, this fact—that you are consciousness and your body is just one of the objects of your awareness—can be realized without an NDE or a psychedelic experience. But just as our eyes cannot see themselves, similarly we always overlook that very consciousness through which we are aware of everything.

For many people in the West this realization—that I can exist without the body—happens through such dramatic events as an NDE or psychedelic experience. Having done extensive research with ketamine, I agree with Jansen that ketamine is a unique substance whose action models the NDE much more than any other known psychedelic drug. With sufficient doses, the conviction that one has died is quite common in ketamine experiences. The sense of being completely disembodied, as well as the intensity of the perceived reality of another realm, leaves no doubt that all this is actually happening.

The acknowledgment that ketamine amazingly models the NDE is the only common point that I share with Jansen. The focus of his paper was to suggest that both NDEs and ketamine experiences are
caused by blockade of N-methyl-D-aspartate (NMDA) receptors. This brings us back to the basic neurological assumption—which is only one of many beliefs about reality—that consciousness is the product of neuronal activity.

Now, who studies NMDA receptors? It is scientists in whose consciousness all these ideas play. If those scientists were not conscious in the first place, who would be speaking about NMDA receptors? So, the truth is the other way around. It is not neurons that produce consciousness; it is consciousness that infuses brain with sentiency and makes neurons work. When consciousness departs, what remains is dead matter.

A few lucky ones will realize spontaneously or with the help of the right teacher that they are immortal consciousness and not a mortal body. Others become convinced of this fact after an NDE or ketamine experience. And those who firmly believe that consciousness is the product of matter perhaps have to wait until the moment of their own death to realize that which is experientially obvious even now.
Commentary on Jansen’s Paper

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ABSTRACT: Karl Jansen raises a fundamental and exciting question: Is mankind’s consciousness the result of neuronal function, or are there extracerebral aspects as well? While his neurotransmitter model of near-death experiences (NDEs) is well described, I find his supporting evidence weak. Methodological differences between studies of ketamine hallucinations and near-death experiences (NDEs) raise doubts about how similar those experiences are phenomenologically. While Jansen’s model has electrifying implications, the data required to support his conclusions do not yet exist.

This long-awaited article by Karl Jansen is a follow-up to his intriguing letter to the British Medical Journal in 1989. His main argument proceeds from assumptions that cannot properly be addressed, given the current state of the literature. He could not raise a more fundamental and exciting question, which is: Is mankind’s consciousness the result of neuronal function, or are there extracerebral aspects as well? It is exciting to see a scientist tackle that issue, using clinical and experimental data to address it. Most previous discussions are speculative and philosophical.

Here comes Jansen, who has the courage to say that there is overwhelming evidence that mind results from neuronal activity; but it is frustrating to realize that most of the references he cites are suspect. This then is the challenge for near-death research. We must start to generate data worthy of the questions we are attempting to answer. Theorists like Jansen need clinical researchers like Raymond Moody and Kenneth Ring; this is the beginning of a dialogue that will blossom into something truly valuable.

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Articles such as Jansen's I believe point the way to the day that funding will be available for large scale prospective studies that will resolve so many of the fundamental issues that Jansen grapples with. For example, he attempts to compare the phenomenology of ketamine hallucinations and near-death experiences (NDEs), yet the studies cited are in no way comparable. This is not Jansen's fault: he is citing the literature as it is. Yet his article highlights the importance of designing studies that will permit proper data that would be helpful in such an article.

Many major scientific advances have resulted from this sort of dynamic. For example, early studies of the histology and function of the hippocampus were confusing and contradictory, often because of differences in experimental technique. Theoretical pressures forced researchers to reanalyze old data and generate new experimental designs that corrected flaws in earlier research, resulting in our current understanding of hippocampal function.

One argument against NDEs being generated by neurotransmitters at the point of death is that it is difficult to understand the evolutionary pressures that would result in the evolution of NDEs occurring to comatose dying persons. Jansen's theory is that neuroprotective agents released by the dying brain also generate an expanded sense of awareness and consciousness. Although he does not specifically articulate the benefits of dying people having NDEs, clearly it would allow for a sense of calm, alertness, and peace, which could result in life-saving action. I once rescued a horse from barbed wire that was threatening to break the horse's leg. Perhaps a similar phenomenon in that horse occurred, as the horse instinctively lay still, did not struggle, and allowed us to rescue it.

Jansen's paper is at its best when it sticks to what can be referenced properly in the literature; but its weaknesses significantly detract from the main point he is making. His neurotransmitter model by itself is well-referenced and described. Its implications are obvious and electrifying. It could trigger tremendous debate, and furthermore, has the power to inspire considerable experimental and clinical research. Jansen further attempts to incorporate this ketamine model into a comprehensive model of the neurobiology of NDEs.

My specific criticisms of his paper relate to his citations of supportive evidence. He states that there is overwhelming evidence that
mind results from neuronal activity, but does not provide substantiating references. He states that all the features of the classic NDE can be produced by ketamine. Unfortunately, we have no standard tool to define the NDE or its classic features. Memories of cardiac arrest survivors and recreational ketamine users are hard to compare from descriptions in the literature, all of which were collected in different ways from examiners looking for different phenomenology and having different biases. Jansen further states that lysergic acid diethylamide (LSD) does not cause NDE-like experiences, again without convincing references. The real problem is that no really systematic study of this has been done, although articles delineating schizophrenic hallucinations from NDEs exist.

Even given this weakness in the literature, Jansen needs to define more clearly and justify his contention that NDEs and ketamine effects are indistinguishable from a clinical point of view. After all, his entire premise is based on this point. Many of the references he cites are not primary sources, but are secondary references themselves. Quoting speculations by Ronald Siegel (1980, 1981), for example, does not properly support his own theory. He does not cite what little work has been done in this area, such as Bruce Greyson's NDE Scale (1983), Kenneth Ring's Weighted Core Experience Index (1980), or the diagnostic work of Brian Bates and Adrian Stanley (1985).

Jansen does not cite enough primary sources of descriptions of NDEs and how those data were collected. He does not describe ketamine hallucinations in detail, or how those descriptions were collected. For example, Scott Rogo (1984) described ketamine hallucinations as having a paranoid flavor to them, and ultimately being dissimilar to NDEs. Although ketamine hallucinations and NDEs might have some areas of overlap, can they be distinguished from one another nine out of ten times, or only one out of a thousand times? Jansen does not address these issues at all.

Jansen's model has the potential to be an enormously important one, one that will be debated for years to come. It could inspire relevant research, from positron emission tomography scans of ketamine users to clinical studies of the phenomena experienced by users of LSD and ketamine and by NDErs. In its present form, there are too many ideas and speculations mixed together. It needs better defini-
tion of what is opinion, philosophical speculations, and a better description of the empirical evidence in the literature.

References


Discussion of “The Ketamine Model of the Near-Death Experience: A Central Role for the N-Methyl-D-Aspartate Receptor,” by Karl L. R. Jansen

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ABSTRACT. We review strengths and weaknesses of Karl Jansen’s approach to the near-death experience (NDE). Strengths include his limited goals and avoidance of the trap of explaining all features of the NDE with his theory, although he surprisingly misunderstood our previously published position. Additionally, we applaud the possible intersection of psychological and biological theories, demonstrated in Jansen’s biochemical explanations for the individualized variations in manifestation and adaptive role of the NDE. However, he failed to take into account the pitfalls in the use of analogy, modeling oversimplification, and in taking association as causality and causes as meaningful, in the arguments for his theory.
We welcome the opportunity to discuss Karl Jansen's paper, which is one more contribution to the growing literature that attempts to explain subjective experience through the use of neurochemical models. Just as previous models of psychosis have used amphetamine and lysergic acid diethylamide (LSD) as the basis of chemical analogues, Jansen has chosen to use the anesthetic ketamine as a model for the near-death experience (NDE). In so doing, he attempted to link physical conditions that have been temporally associated as precipitants of NDEs, particularly hypoxia and related blood gas abnormalities, ischemia, hypoglycemia, and temporal lobe epilepsy.

We certainly do not need to remind him that temporal association with a variety of different physical and psychological precipitants does not prove a causal relationship. In the same vein, a chemically analogous state does not in any way provide conclusive evidence for the causation of a naturally occurring psychological phenomenon such as the near-death experience. We do not intend to review the logical arguments concerning problems inherent in such models except to point out that analogical reasoning, although tempting to invoke, is fraught with interpretive difficulties when not acknowledged as such.

In general, we find that Jansen's hypothesis has considerable appeal and is deserving of serious study. He wisely eschewed any effort to explain all NDEs based on the glutamate hypothesis. Indeed, he ended up reaching the same conclusion that we did more than a decade ago (Gabbard and Twemlow, 1984) that the NDE is probably the final common expression of several different causes. Indeed, we see a possible intersection between our own psychoanalytic perspective and Jansen's neurochemical model.

As we have noted previously (Gabbard and Twemlow, 1991), often people who think they are near death when they are not even in serious jeopardy may nevertheless have a near-death experience. We suggested at the time that the thought of death as well as the physical threat of death can precipitate an elaborate psychological defense mechanism activated by this perception, however misguided it may be. This defensive effort has as its goal the eradication of anxiety and the replacement of that anxiety with a soothing state of mind. In keeping with the principles of overdetermination and multiple causation, the precipitant can be conscious or unconscious in nature.

Moreover, research on near-death experiences in children (Gabbard and Twemlow, 1984) has demonstrated that young children who have no concept of death are nevertheless capable of having near-death
experiences. Death is omnipresent in the human psyche, however, and although an infant may have no concept of death, it certainly has a sense of dread. In other words, having emerged from the pain of birth itself, the baby screaming with hunger and demanding to be fed cannot name the catastrophe that is feared, even though a terrible threat is experienced. This primitive dread is what Wilfred Bion referred to as catastrophe (Bion, 1963). We postulated that all of us live with the unconscious awareness that a disaster from out of the blue may snuff us out at any moment and that this reality never entirely disappears from our thinking.

In Bion’s view, faith is what enables us to get from one moment of catastrophe to another while maintaining some semblance of sanity. The imagery of the near-death experience reflects this faith in that a catastrophe is transformed into a beautiful transcendent event. In speculating about the origins of the adaptive defense mechanism of the near-death experience, we considered the contribution of genetic factors, and it is possible that Jansen’s hypothesis may help to clarify some of the biochemical underpinnings of the psychological defense. Specifically, the full-blown NDE might be a subjective response to neuroprotective chemicals that prevent the toxic effect of glutamate flooding. Given the ubiquity of the threat of death, no great leap of imagination is required to speculate that there could be considerable survival value in such a feature within the human genome.

In a previous paper, we concluded, “The dread of oblivion is not an issue that rears its ugly head only when one’s survival is literally threatened. It is background noise that haunts us day and night as we frantically strive to deny our own mortality through a myriad of self-deceptions” (Gabbard and Twemlow, 1991, p. 46). Jansen may have found a biological metaphor for the way in which the human brain adapts itself to the sometimes extreme conscious and unconscious stresses of life that we view psychologically as defensive processes.

Having applauded the creativity of his thinking, we would now like to turn our attention to what we view as some limitations of Jansen’s model. Central to his perspective was the following line of reasoning: Some of the conditions temporally associated with NDEs release a flood of the chemical glutamate, which can, if unmodified, result in death of neurons. This neurotoxicity is blocked by ketamine, resulting in a dissociative NDE-like state. He then postulated that in certain individuals who are not under the influence of ketamine,
particular substances may bind protectively to the same receptors to prevent toxicity to neurons. Thus the theory implied a unique mechanism for release of as yet unidentified brain chemicals that block the neurotoxic effect of glutamate. Jansen noted that this hypothetical defensive flood of substances to prevent cell death was the only speculative aspect of his model. Be that as it may, his entire model pivoted on this highly speculative point! Because the paper was replete with impressive scholarship, a casual reader may come away with the impression that the model is a great deal less speculative than it actually is.

Also, at times Jansen glossed over highly controversial issues with deceiving oversimplification. Consider, for example, his statement that "there is overwhelming evidence from thousands of studies relating brain events to alterations in mental state that 'mind' results from neuronal activity" (p. 6). In this rather glib statement Jansen has reduced the complex evidential and philosophical issues involved in the mind/body problem to a rather simple matter: What we know as mind is the result of neuronal activity. This view does not address rigorous critiques of this idea, such as that of John Searle (1992), who made a persuasive case that while states of consciousness may be properties of the brain, they certainly are not reducible to neural activity. The essence of "mind" in Searle's view is consciousness. He noted that materialist perspectives on the concept of "mind" systematically omit conscious experience either by identifying it with something else that is not directly related to consciousness or by leaving it out entirely. There is a fundamental difference between conscious phenomena and neurophysiological phenomena that makes it impossible to reduce consciousness to neuronal activity alone. Consciousness can never be described from an "objective" third-person perspective and is therefore ontologically subjective. Searle also eschewed Cartesian dualism, and he suggested that the irreducible nature of conscious states does not imply a dualistic view. He emphatically stated that materialism and dualism are not the only choices to deal with the mind/body problem. One does not need to choose between them, and the polarization between dualistic and materialistic assumptions is archaic, in Searle's view.

Blurring this distinction between the realm of the psychological and the realm of the biological created further difficulties in articulating Jansen's model. A thought can act as a stressor for the glutamate flood, just as dramatically as any external or physiological event. Researchers studying posttraumatic stress disorder (PTSD)
have repeatedly observed that a cognition related to the meaning of a trauma can precipitate the symptoms of posttraumatic stress disorder, which obviously have neurophysiological correlates. Those flashbacks produced in PTSD are characterized by richness, complexity, and idiosyncratic meanings that are not fully reducible to chemical explanations.

Jansen has failed to distinguish clearly between causes and meanings. Neurochemical phenomena can be interpreted in a variety of ways, depending on the meanings attributed to them by a particular individual's unique psychological features. The examples used by Jansen illustrate this point compellingly. He quoted Stanislav Grof, for example, as saying, "If you have a full-blown experience of ketamine, you can never believe there is death or that death can possibly influence who you are." Yet clearly not everyone has the reaction described by Grof. As Jansen himself noted, only 30 percent of normal subjects given ketamine thought the events had really happened. The majority, in other words, recognized it as a dream or hallucination rather than an experience that transcended death. In fact, even though Jansen did not say much about his own experiences on ketamine, or his own NDEs for that matter, his article clearly made the point that he himself viewed the NDE as an analogue of a ketamine-induced hallucination rather than a mystical state that eliminated his fear of death.

The point we wish to stress here is that the psychological meanings construed in a unique way by each individual cannot be reduced to neuroscience explanations. If one wants to learn about music, one does not begin by visiting a piano factory.

Jansen's tendency to miss the subtlety and complexity of human experience was again in evidence in his discussion of the criteria of the NDE. In a critique of our discussion (Gabbard and Twemlow, 1989) of the previously published model advocated by Juan Saavedra-Aguilar and Juan Gómez-Jeria (1989), Jansen stated that we required all features of an NDE, both usual and unusual, to be explainable by a unitive theory. In fact, we claimed exactly the opposite. Saavedra-Aguilar and Gómez-Jeria appeared to be claiming to explain all relevant scientific evidence with their model. We simply pointed out some exceptions, such as NDEs occurring in low stress situations. We agree that near-death experiences are not unitive nor is it necessary to make them unitive. We noted in that discussion, as we do here, that the principles of multiple causation and overdetermination must be taken into account to explain psychological phe-
nomena. Our point was that the model was too general in its attempt to explain virtually every aspect of the NDE.

Throughout his paper, Jansen had a tendency to state what he believes as though it were true by fiat. For example, he wrote, “As might be expected in a mental state with a neurobiological origin, more mundane accounts also occur, such as children who may ‘see’ their schoolfellows rather than God and angels.” It is not apparent to us why this would follow logically from a state that has a neurobiological origin. From our perspective, psychological issues related to the child’s developmental phase would more likely determine the fact that some children see schoolfellows (Gabbard and Twemlow, 1984). Again, in our view, Jansen indulged in an unnecessary and unfortunate oversimplification in light of the highly focused content and thrust of his paper. Certainly, the near-death experience is highly variable from person to person and culture to culture (Gabbard and Twemlow, 1984). For example, the tunnel and the being of light in East Indians are often depicted as the River Ganges and a specific guru. In other words, the content and meaning of an NDE are certainly determined as much by intrapsychic factors and by cultural experience as they are by biology.

Near the end of his paper Jansen succinctly summarized a variety of hypotheses for NDEs and then applied his model of protection against glutamate neurotoxicity to see if that model “fit” with the relevant hypothesis. These applications are sketchy and certainly not convincing. Jansen did draw a useful analogy between neurotoxic and neuroprotective mechanisms in his discussion of temporal lobe epilepsy, but in the discussion of whether endorphins can produce NDE-like hallucinogenic phenomena, he criticized evidence that certain beta-endorphins have epileptogenic effects. The main thrust of his argument was that experiments with rats cannot be translated to the human situation. This thinking, however, did not stop him from drawing analogies to dogs, who he said have endorphin release associated with death.

Although we have outlined a handful of criticisms of the model, in closing we wish to reiterate our admiration for the scholarly and original work that Jansen has presented here. It is best viewed as a piece of a larger puzzle rather than the solution to the puzzle itself. Nevertheless, we can congratulate Jansen on his contributions to the field and hope that research will be stimulated by his thoughtful essay.
References


Comments on “The Ketamine Model of the Near-Death Experience: A Central Role for the N-Methyl-D-Aspartate Receptor”

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ABSTRACT: Although ketamine can induce a state similar to a near-death experience (NDE), there is a striking difference between experiences induced by ketamine used in a recreational context and in an operating room. Ketamine is a noncompetitive antagonist of the N-methyl-D-aspartate receptor, as is ibogaine, the main alkaloid of a shrub used in Central Africa to induce NDEs in a religious context. Ibogaine can also elicit different experiences when used in a hallucinatory context or in initiatic rituals, where a superficial state of coma is induced. These data raise the question of whether the chemically-induced NDE-like experience is related to the use of a particular kind of substance or to a genuine comatose state.

The hypothesis devised by Karl Jansen on the role of N-methyl-D-aspartate (NMDA) receptors in near-death experiences (NDEs) is fascinating and very attractive, especially for those who, like myself, have always worked on the neurochemical and neurophysiological aspects of altered states of consciousness (ASCs). But this hypothesis is particularly fascinating because the identification of NMDA receptors as an essential neurochemical target in the development of an NDE allows interesting convergences with other neurophysiological models to be established, such as those of Daniel Carr (1982) and Juan Saavedra-Aguilar and Juan Gómez-Jeria (1989), and for the

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first time allows a sort of "global vision" of the neurophysiology of NDEs.

Jansen, after having defined the hypothesis that the NMDA receptors are involved in the genesis of an NDE, rightly focused his attention on the possibility of provoking this type of experience through a chemical manipulation of the NMDA receptors. The most interesting chemical substance in this regard appears to be ketamine. It is true that NDEs have been associated with a great number of hallucinogens, including hashish (Siegel and Hirschman, 1984) and lysergic acid diethylamide (LSD) (Grof, 1994), but ketamine, an anesthetic still routinely used in surgery, has especially been associated with a high rate of NDEs (Rogo, 1984).

Ketamine was first synthesized in 1963, the first laboratory data date back to 1965 (McCarthy, Chen, Kaump, and Enson, 1965), while the first pharmacological data on humans were published by Edward Domino and associates (Domino, Chodoff, and Corssen, 1965). It was Domino's team who coined the term "dissociative anesthesia" to denote the particular state provoked by the injection of 1 to 2 milligrams (mg) intravenously or of 3 to 5 mg intramuscularly in patients; to describe this state they used the term "trance-like". However, it was immediately clear that the use of this drug was associated with a high number of "postanesthetic emergence reactions," the term used for an extremely varied range of psychological reactions, ranging from panic attacks to hallucinatory states, from temporal and spatial disorientation to genuine psychotic reactions. These states, especially when ketamine was used alone, affected 13.3 percent of patients (Parke-Davis and Co., 1969) and were soon interpreted as an organic cerebral toxicosis (Henry and Mann, 1965), though in the scientific literature their definition has been rather vague and they have been given other labels such as "sensory deprivation," "hallucinations," "pseudohallucinations," and "delirium" (Sedman, 1966).

This confusion in terminology has at times led to classifying ketamine among the hallucinogens, even if its psychophysiological effects are very different from the molecules usually defined as such. For example, comparing LSD with ketamine, it can be noted that the former induces a decrease in voltage of the electroencephalogram (EEG); there is an acceleration of activity; it does not produce anesthesia; it inhibits food intake; and it always causes phenomena of tolerance and a state of abstract hallucinations independent of reality with a strong perceptive component. Ketamine, on the other hand, induces a state characterized by an increase in EEG voltage, a slow-
ing down of activity, and a deep anesthesia; it stimulates the appetite centers; it often provokes a retrograde amnesia; it never induces phenomena of tolerance; and the type of psychological effects induced largely depends on the environmental stimuli, with a marked action on proprioceptive perception of the individual's body. The psychological effects, and also the neurochemical target—serotonin receptors in the case of LSD and NMDA receptors in the case of ketamine—appear to be completely different.

However, the classification of ketamine as a hallucinogen led, in the past, to its being used illegally both by means of intramuscular injections in doses of 1 to 2 mg and taken orally in doses 8 to 10 mg, by young people, seeking the psychedelic effects, considered undesirable in anesthesiological routine (Jansen, 1993; Johnstone, 1973). The frequency of anxiety or negative reactions led to the notion that the substance induced "bad trips" too often, and thus its use gradually became limited to highly restricted circles, to the extent that to date there is only one documented case of psychological dependence on this substance (Hurt and Ritchie, 1994). The material available today in the underground literature on this substance contains some useful information for the purposes of our analysis, corroborated by a number of my own attempts to induce an NDE through an intramuscular injection of ketamine.

It in fact appears that the recreational use of this substance may induce some components of an NDE, in particular the tunnel experience, the sense of hovering above one's own body, and the vision of a bright light (Moore and Alltounian, 1978), but these effects nevertheless seem to remain confined to the level of the intrapsychic world of the experiencer and are consequently experienced as "visions" or "hallucinations," lacking that sense of reality that is typical of the NDE. Furthermore, they are deprived of the strong emotional component that makes an NDE so important in the life of the individual experiencing it. This sense of reality and emotional involvement are, on the other hand, present in some subjects who have experienced the effects of ketamine during anesthesia (Collier, 1972), which is in fact a state of pharmacologically piloted coma, raising three interesting interpretative hypotheses.

First, the action of ketamine on NMDA receptors presents interesting analogies with what occurs during an NDE, which, given its complexity, nevertheless remains a distinct phenomenon with respect to the simple pharmacological action of this anaesthetic. Second, ketamine is capable of inducing a common experience that, when
there is real danger to life, is experienced as an NDE, and otherwise as a simple "hallucination." Third, ketamine may induce a threshold experience that takes the subject close to a real NDE; the context in which it takes place is decisive in deciding whether it will trigger an NDE or not.

Whichever interpretation we incline toward, the importance of NMDA receptors cannot easily be set aside, especially in relation to the use of another substance: ibogaine. Ibogaine, the most important alkaloid of the plant *Tabernanthe iboga*, an Apocinacea of Central Africa, was isolated in the 1950s by French and Swiss chemists (Goutarel, Gollhofer, and Sillans, 1993). Renewed interest has recently been shown in ibogaine, especially in relation to its anti-addiction activity with regard to heroin, cocaine, amphetamines, nicotine, and alcohol (Lotsof and Sisko, 1991). Due to this unique pharmacological activity, ibogaine has been actively investigated in recent years and today we know that it acts on the dopaminergic system (Glick, Rossman, Dong, and Keller, 1993), on the serotonergic system (Sershen, Hashim, and Lajtha, 1994), on the mu-opioid receptors (Deecher, Teitler, Soderlund, Bornmann, Kuehne, and Glick, 1992), and on NMDA receptors (Popik, Layer, and Skolnick, 1994). This last action has been shown in a recent review (Popik, Layer, and Skolnick, 1995) to be one of the most important for the purposes of its anti-addiction activity, which furthermore appears closely connected with the psychological, and therefore psychotherapeutic, effects of the substance (Sheppard, 1994).

This leads us to consider the traditional use of the plant in Central Africa, where it has been used for centuries by the Pigmy, Bakota, and Bakwele tribes of the Congo, southern Cameroon, and eastern Gabon in a series of initiatory rites aimed at giving the members of the tribe a vision of the meaning of life and death in the passage from adolescence to adulthood. Subsequently the use of the plant spread to the Fang populations who, in more recent times, invaded Gabon from the north, where its use has given rise to a remarkable syncretist cult, rich in Catholic elements, known as Bwiti, considered today as the main religious form of this ethnic group. As I was able to observe during a recent trip, the use of iboga in the initiatory rites of the Bakota, the Bakwele, and the Pigmy is today strongly on the decrease, due to the rapid processes of acculturation of these tribes and the spread of new cults of possession from the East, while it maintains all its vitality within the Fang culture, in a highly culturally contaminated and acculturated context.
The experience induced in Africa by taking strong doses of *Tabernanthe iboga*, doses capable of inducing a state of superficial coma, could be classified as an NDE without any difficulty: amongst the tribes of eastern Gabon it is interpreted as meeting the ancestors, whether men or animals; while among the Fang ethnic groups it is frankly defined as “meeting God.” Personally, I have been present only at a ceremony of the Bakota, in the Makoukou district in the far east of the Gabon forest, where three girls volunteered to take part. The bark of *Tabernanthe iboga* root was administered to them for a period of more than two days, until on the second night two of them fell into a state of coma of a superficial type, as all their physiological parameters were normal. On awakening, they described an experience that may be summarized as follows:

(a) separation of the spirit from the physical body and gradual upward ascension;
(b) overcoming a series of obstacles such as rivers and fire, or temptations such as banquets where meat, which subsequently turned out to be human flesh, was plentiful;
(c) encounters with dead relatives who gave each young girl advice on her future life; and
(d) for both girls, the experience came to a climax with an encounter with a leopard glowing with a shining, golden light, considered the totem animal of the whole Bakota ethnic group, which gives young girls the magic power that ensures that they will have many children, or in some cases the power to heal.

The day following this experience each young girl’s behavior was trance-like, being possessed repeatedly by the spirit of the leopard. This component of possession appears to a somewhat lesser extent in the Fang ceremonies but raises interesting analogies between this type of experience and the physiology of states of possession, at times due to an activation of the right temporal limbic system (Peters and Prince-Williams, 1983).

This experience seems very similar to that reported by several anthropologists who have studied the Bwiti rites among the Fang. James Fernandez (1982), for example, in his monumental work on the Bwiti of the north of Gabon, reported numerous visions by the initiates, of which he highlighted a number of common elements:

(a) the separation of the spirit from the physical body;
(b) contact with the dead, often relatives of the initiate;
(c) journeys in afterlife worlds and landscapes, within which there are often obstacles to be overcome;
(d) the climax of the experience is the contact with a bright power of divine nature, a concept that is in contrast absent from more ancient aboriginal contexts.

Stanislaw Swidersky (1990), who has, on the other hand, worked primarily with the Bwiti of the estuary where the signs of Christian acculturation are strongest, confirmed the general pattern, although in this case contacts with "spiritual guides," taken from Catholic iconography, become predominant and the natural landscapes of the forest are often replaced by journeys in "cities of light" located in afterlife worlds.

Of course, beyond the contents, which may vary due to cultural background, the initiatory experiences induced by iboga, while they stress the importance that substances acting on NMDA receptors may have, cannot be regarded as evidence in favor of an organic hypothesis of the NDE. The African initiation ceremonies involve the use of large quantities of the substance, which provoke, as mentioned above, a real, if superficial, state of coma; and, although rarely, this state may become irreversible for the neophyte, ending in death (Fernandez, 1982; Swidersky, 1990). Furthermore, once initiated, the initiate will take iboga periodically, but never again in such concentrated amounts, resulting in experiences that may easily be defined as "hallucinatory" but are very different from the initiatory journey, which, for many aspects, recalls the difference between the experiences induced by recreational doses and anesthetic doses of ketamine.

In conclusion, the similarity between ibogaine and ketamine, both of which are substances acting on NMDA receptors, and their capacity to provoke an NDE at certain doses and in an appropriate context, underlines the importance of NMDA receptors in the complex physiological picture that probably accompanies an NDE, even if it leaves the interpretative hypotheses that we had previously formulated without an answer. Are they chemical substances effectively capable of provoking an experience that is the same as an NDE? Or rather, do they provoke experiences similar to an NDE but distinguished by a number of fundamental characteristics, related or not to a real danger to life? Or do these substances perhaps activate some neurochemical mechanisms that lead the subject to a sort of threshold experience, which may be experienced as a simple hallucination if it
is experienced recreationally or evolve towards a real NDE if there is a real physiological state of coma induced for religious or medical reasons? The importance of Jansen's article is that it established for the first time a point of convergence between various neurophysiological hypotheses of NDEs, even though a greater amount of data will be necessary to establish to what extent and in which way this model is effectively correlated with such experiences.

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ABSTRACT: The commentators on my paper raised several interesting issues. Set and setting do influence drug effects, but they also influence near-death experiences (NDEs). Some NDEs are very anxiety-generating, just like some ketamine experiences, though frightening NDEs have been ignored by most researchers. High frequency, compulsive ketamine use is rare. While dimethyltryptamine (DMT) may induce NDEs, this is far from typical, while NDE-like effects are typical of ketamine. Rapidity of onset is not related to the capacity of a drug to induce NDEs. The reality of endopsychosins is doubtful, but the reality of N-methyl-D-aspartate (NMDA) blocking mechanisms is not. NDEs and dream sleep may involve similar mechanisms. Altered states of consciousness do not require a normally functioning brain. Finally, I discuss the possible evolutionary advantage of the NDE mechanism.

I would like to commence by expressing my gratitude to the seven commentators for the time and effort taken with these valuable and interesting commentaries.

Response to Rick Strassman

Rick Strassman began with a discussion of self-experimentation as a valuable and long-standing tradition in medical research. While this is a view that I share, regrettably many others do not, for rea-
sons related both to the overvaluation of statistics, which can conceal as much as they reveal, and to the prevailing sociocultural attitudes towards altered states of consciousness induced by substances. These attitudes are currently reflected in law. Remaining within the law and contemporary ethical guidelines is a requirement that places strict limits upon such research. While it was possible for William James to write of his explorations with consciousness-altering substances in some detail, it is doubtful whether a contemporary professor of psychology at Harvard could do so without censure.

The second major focus is a comparison of the "classical" psychedelic agents, such as lysergic acid diethylamide (LSD), with ketamine. With respect to differences between ketamine-induced states and near-death experiences (NDEs), the central observation is that ketamine is a drug and as such the effects are partially susceptible to set and setting. Ketamine can of course produce states of mind other than NDEs, just as persons who have a myocardial infarction may report altered states of consciousness with a variety of contents, many of which would not be considered to be classical NDEs. The NDE is only one of a spectrum of effects. Scott Rogo has provided an interesting discussion of this issue (Rogo, 1984).

An interesting way to investigate some of these issues would be to administer ketamine and a "classical" psychedelic such as di-methyltryptamine (DMT) to persons who have and have not had NDEs, in double-blind controlled studies. Unfortunately, it is exceptionally difficult to obtain the necessary permissions to do such research in the present climate. Indeed, even the administration of the prescription drug ketamine for nonmedical purposes is a difficult undertaking in some countries, despite its excellent safety record. Accordingly, we are largely reduced to a reliance on the available literature, which leaves little doubt that ketamine does induce a mental state distinctly different from the substances described as classical hallucinogens. Franz Vollenweider has recently described a series of experiments in which subjects were given d-amphetamine, racemic ketamine, S- and R-ketamine, and psilocybin. Positron emission tomography (PET) brain scans were carried out, and altered states of consciousness assessed using the Altered States of Consciousness Questionnaire, the Ego Pathology Inventory, and the inventory of the Association for Methodology and Documentation in Psychiatry (Vollenweider, 1996). While Vollenweider's studies did not specifically address the issue of NDEs, the results tended to support ketamine
as the drug that reproduces effects most like those of NDEs (see also Vollenweider, 1994).

Strassman argued that one of the differences between NDEs and ketamine anesthesia is that “emergence phenomena” are often unpleasant and there is no desire to repeat them. However, anesthetists have demonstrated that attention to set and setting can make them pleasant. It is also important to recall that some NDEs are not pleasant nor desired to be repeated either, in response to the set and setting in which the NDE occurs. Although some authors have romanticized NDEs, if we listen with an open mind it is quite clear that a substantial fraction are frightening rather than tranquil. This is best seen where persons completely outside the “NDE debate” describe their experiences, as did Marianne Faithfull, former consort of musician Mick Jagger. In her autobiography, Faithfull described several classical but unpleasant NDEs occurring in the context of the end of her relationship with Jagger and the death (possibly by murder) of their friend Brian Jones (Faithfull and Dalton, 1994).

The reason unpleasant NDEs are not often given their due place is that some authors have already made up their minds that NDEs are tranquil by definition, and that if the person describes a frightening experience, he or she cannot have had an NDE. This is a rather limiting perspective, and introduces considerable subjective bias into some books about the NDE. Even if we were to abandon the scientific paradigm completely and accept that NDEs in fact occur during a state of soul transition, our whole experience of the universe is such that we would expect some darkness to accompany the light, one being required to define the other. Even if spiritual explanations are true, it is likely that some NDEs will be perceived as far from pleasant in some persons. Many of the ancient myths and religious ideas have maintained that an experience of a rather unpleasant character was a definite possibility. For example, a substantial fraction of The Tibetan Book of the Dead concerns fearful experiences:

A second sign of Third Bardo existence are experiences of panic, torture and persecution... [T]he form that these torturing demons take will depend on the person’s cultural background. (Leary, Metzner and Alpert, 1964, p. 80)

If there were indeed a period of “soul transition,” the assertion that this would be universally tranquil is pushing credulity too far. Peter Fenwick addressed the issue of selection bias in his commentary, noting that persons who have had frightening or neutral expe-
periences are much less likely to want to communicate them than those who have had positive experiences.

Strassman's statement that ketamine is "highly addictive" requires some qualification, and is difficult to reconcile with his statement in the preceding paragraph about the frequently observed desire not to repeat the experience, even allowing for the different contexts of use, anesthetic versus recreational, to which the two statements refer. While there have been famous cases of severely compulsive, excessive ketamine use, these are rare and as such are often the subject of special comment, just as with the classical psychedelic drugs, where continual use is considered to be highly unusual but is nevertheless seen in some persons. The example of John Lilly is a case in point. The account in his autobiography (Lilly, 1978) suggested a highly unusual person who had a need to re-experience the near-death state continually, either through ketamine or by long periods in a flotation tank, in a way that did not actually produce death.

It is also worth noting that Lilly managed to produce a series of NDEs for himself in which real death was imminent by "accidental" actions that an analyst might regard as disguised suicidal acts: for example, going for a bicycle ride down a mountain while under the influence of a phencyclidine (PCP)-like drug, and having a collision with a truck resulting in weeks in the hospital; intravenously injecting a soap bubble together with some LSD in a hotel room, again resulting in hospital admission (the bubble had lodged in his visual artery); passing out in a puddle from which he was saved at the last minute; and so on. It is possible to argue that there are definite similarities between Lilly's seeking of ketamine-induced NDEs, and what appears to have been a compulsive flirtation with real death, resulting in "real" NDEs. Nor is it necessarily true that one action is conscious, the other unconscious. Those persons who do become compulsive ketamine users appear to be as out of control of their actions as a person unconsciously driven to flirt with death. It is of interest to recall the horrific fate of Marcia Moore, the astrologer who co-wrote Journeys Into the Bright World (Moore and Alltounian, 1978), a book about her adventures with ketamine. There are several chilling statements in the book that suggest a person with an unconscious determination to open Bluebeard's cupboard. Moore was found murdered in a forest after the book was completed.

For many people, one ketamine experience, just like one NDE, appears to be more than enough, and the lack of a compulsive desire to repeat the experience is a feature that ketamine and NDEs have
in common, rather than a point of distinction. It is also true that most persons who have experienced NDEs do not have the means to reproduce them safely, and are thus unable to engage in a process such as that described by Lilly, whether they wished to or not. In general, the use of almost any drug, or indeed almost any human behavior, can become excessive and compulsive in predisposed individuals who are able to practice the indulgence.

Dissociation and dreamlike imagery certainly can occur with classical psychedelic drugs, but it is still clear that in most cases the quality is distinctly different from that produced by the dissociative anesthetics, and that it is ketamine that more reliably reproduces the quality of the NDE, and not psilocybin, DMT, LSD, or mescaline. These latter drugs are not generally regarded as dissociative agents that typically cause NDEs although, as stated in my article, they can certainly do so on occasion. This is because the individual brain can sometimes respond to drugs in markedly idiosyncratic ways, just as immune systems can demonstrate idiosyncratic responses to allergens. There are rare persons who are put to sleep by cocaine, others who are roused by diazepam. Strassman described as outstanding examples of such individual variation two persons who had minimal responses to a high dose of intravenous DMT.

There may be some brains in which LSD and its relatives have neurochemical actions that result, downstream, in N-methyl-D-aspartate (NMDA) receptor blockade, but this is far from the norm. It is possible that there will be some brains where drugs with a primarily serotonergic action such as DMT do result in NDEs. We must always bear in mind the variation in individual response that is possible. The arguments in my hypothesis are for the general case, and certainly allow for exceptions such as DMT-induced NDEs.

The comments concerning rapidity of onset are of interest. Nonmedical ketamine is usually taken orally in the United Kingdom, and usually by mistake, with the users at first believing themselves to have taken another drug, as ketamine is sold fraudulently as the drug methylenedioxymethamphetamine (MDMA), popularly known as Ecstasy. This provides an opportunity to study the effects of the drug in what is almost a double-blind naturalistic study. In brief, the effects of oral ketamine are eventually the same as when it is injected, including the induction of NDEs. Injecting ketamine is relatively rare in the United Kingdom.

PCP also produces an excellent model of the NDE. PCP can result in a state where the consumer believes that he or she is dead for
several hours. It is a congener of ketamine, both drugs being aryl-cyclohexylamines, and the ion channel on the NMDA receptor has been named after it. PCP is usually taken orally, which would tend not to support an argument that the rapidity of action is an important feature in whether or not a drug will produce an NDE.

The experiences reported from DMT studies are of interest. The definitive study would administer ketamine to the same persons and examine the differences. It is possible that compulsive use of DMT is rarely seen simply because of the rarity of the drug. Availability has a close relationship to who becomes a compulsive ketamine user and who does not. Indeed, availability is a key issue in any form of addiction. Historically, we have often been proven wrong in predicting that a particular drug is free from the risk of compulsive use as the drug became more available. A recent example of this error was the claim made in this respect for MDMA in the 1980s. My research subjects include a person who injected 250 milligrams of pure MDMA powder four times a day, intravenously, for over six months.

No doubt those involved in the early research upon ketamine and its effects would have been astounded by the level of use engaged in by Lilly, as many persons still are today. It seems reasonable to predict that eventually availability and predisposition to compulsive use will coincide in the case of DMT, if this has not happened already.

Endogenous NDE-Generating Substances

The brain is a very complex organ, and most mental states have multiple determinants. There are different routes to the same outcome. Thus, for example, a dopamine-releasing agent has a downstream effect upon glutamate release, which is reduced. The central tenet of my hypothesis is that most NDEs result from a reduction in glutamatergic transmission, probably achieved through NMDA receptor blockade in certain pathways in particular parts of the brain. However, the means by which this blockade is brought about is certainly the most speculative part of the hypothesis, and it is highly probable that it could be achieved by several different routes. Certainly the specific compounds labeled “endopsychosins” in the 1980s have little experimental verification of their existence or importance in the human brain. I wished to use the term in a wider sense, to include any endogenous substances that act as NMDA receptor antagonists. As I pointed out in the hypothesis, it may be that an ion
such as magnesium or zinc is responsible for the NMDA receptor blockade, or some other as yet undiscovered chemical, ion, or indirect process, such as the action of some other neurotransmitter system. The complexity of this receptor macromolecule suggests that the answer to its regulation can never be a simple matter, like the endogenous ligand that was almost immediately discovered for cannabis (THC) receptors.

The case for the existence of DMT in the brain is certainly much stronger than that for the endopsychosins, but this does not dispel the very substantial evidence implicating NMDA receptor blockade in the NDE, however this is achieved. Substances such as DMT may play a role in some part of what will certainly be a multisystem, interactive process. Current evidence, however, does not suggest that DMT itself will be shown to play a central role.

Strassman has made a very valuable contribution to quantifying unusual mental states, and we can only hope that the bodies that control research in these areas will allow this contribution to be more widely applied.

With respect to the religious/philosophical issue, of course the NDE may be studied within these branches of inquiry. However, they are simply not the branches with which my hypothesis is concerned. We would not expect a discussion of neurochemistry from a philosopher or a priest, and why should we? These are simply different paradigms. Why should the person who studies how a radio works also offer a critique upon the music? To fail to do so is not an attempt to rob the music of its beauty, nor does it suggest that we are uncomfortable with music. There is no question that the human mind has a very important, brain-generated capacity for religious experience; there is no ambivalence here of any kind, nor the slightest discomfiture. We are surrounded by religions and their symbols. Of course we routinely use religious and spiritual terms. By the term "nonreligious," I simply meant that I do not adhere to any of the particular systems of beliefs identified with organized religion, and as such the distinctly Dante-esque/Catholic flavor of these NDEs is of interest. Stuart Twemlow and Glen Gabbard might explain this as due to sociocultural forces, and I would agree with them. As Carl Jung pointed out, it is not possible to divorce ourselves from the religious/spiritual aspects of the psyche, which are an integral part of the human package. There can be no doubt that this religious dimension will at some level influence our thoughts and vocabulary to add meaning to our lives. The error occurs when we project this
inner religious aspect onto the external environment, and really expect to encounter our gods and goddesses in external reality. Many lives have been lost in the name of these projections.

Strassman stated that “the adaptive or biological significance of an endogenous NDE-ogen is difficult to discern.” In fact, I discussed the significance of the “endogenous NDE-ogen” in considerable detail in my hypothesis. The major function of such an agent in the glutamate hypothesis of the NDE is that it will protect the brain from excitotoxic cell damage, while generating a mental state that has valuable psychological aspects, such as holding overwhelming anxiety at bay—the usual function of less severe dissociative phenomena in psychology. The psychological advantage may be even greater where the forces of the unconscious are harnessed to give the person a strong message to go back in terms of a mythological drama, and that it is “not their time”—the final expression of the deep drive in the psyche to survive, presented by those parts of the brain still able to produce such a phenomenon. If we consider how much of our brains we can lose in head injuries and yet return to near-normal functioning, and how little electrical activity is recorded during stage 4 sleep and yet the awakened sleeper sometimes records highly significant dream fragments (Kales, 1987; Lask, 1988), it becomes possible to conceptualize the ailing brain screening this final drama, even though there may be very little activity remaining insofar as current instruments are able to detect it. As those who have NDEs do not in fact die, the evolutionary advantage is tremendous.

Response to Peter Fenwick

Fenwick recorded that he and his wife rejected NDEs that were reported to have occurred while the person was asleep. However, NMDA receptor blockade is also central to the dreaming process, as this also involves sensory deprivation accompanied by an absorbing inner drama. It could be argued that some NDEs result from an activation of the dreaming mechanism, and that alterations in glutamatergic function in certain areas are central to this. Accordingly, there is no need to limit the glutamate hypothesis to a subset of NDEs occurring in catastrophic circumstances. While this subset is useful for highlighting the key issues, the fact remains that glutamate and NMDA receptors play a central role in the brain under all circumstances, and the conditions that activate particular subpro-
grams are only poorly understood. One of these is the prevention of excitotoxic damage, but there is no reason to suppose that the NDE mechanism would never be activated spontaneously. Indeed, as an expert in epilepsy, Fenwick will be familiar with the sudden onset of major neuroelectrical changes in the brain while persons are “awake and relaxed, when depressed, and in minor infections and in routine anesthesia.” When we consider that the brain, and body, can have major seizures “out of the blue,” it is not difficult to conceptualize activation of the NDE-generating mechanism in the absence of catastrophe, or indeed any apparent explanation outside of the functioning of the brain itself.

It is of interest to consider also the example of schizophrenia. It is entirely possible to have auditory and visual hallucinations with no apparent precipitating factors whatsoever. An increasingly large number of neuroscientists now believe that the central abnormality in schizophrenia lies in underactivity of the glutamatergic system, with overactivity of dopamine as a variable downstream effect. This is because brain imaging studies show damage in parts of the brain that primarily rely upon glutamate as a neurotransmitter, such as the parahippocampal gyrus. It is of interest to note, in this context, that ketamine increases dopamine but not serotonin concentrations in the blood (Krupitsky, Grinenko, Karandashova, Berkaliev, Moshkov, and Borodkin, 1990), and that ketamine is being explored as a model of schizophrenia (Krystal, Karper, Seibyl, Freeman, Delaney, Bremner, Heninger, Bowers, and Charney, 1994). With respect to the “reality” of ketamine experiences, almost all persons believe their experiences to be real while under the influence of the drug. In one study 30% of the subjects continued to insist on the reality of their experiences once the drug had worn off.

With respect to the issue of consciousness and a “dysfunctional” brain, some assumptions have been made about the meaning of the terms “clarity,” “consciousness,” and “dysfunctional,” which must be examined. It is useful to consider again the examples of schizophrenia and dreaming. In many cases of schizophrenia, consciousness and clarity appear to be normal, yet there is evidence of brain dysfunction. In dreaming, a very different consciousness and brain organization pertain from that seen in waking, and there is little “clarity,” yet we do not say that the brain is dysfunctional, nor do we find it impossible to remember our dreams or ascribe meaning to them. Certainly I would agree with Fenwick that as cerebral function becomes compromised it becomes disorganized, if this term means that it is...
not organized according to its normal waking principles. But there are other ways in which the brain and mind can be organized, and the lesson from mind-altering drugs is that “clarity” in what Lilly referred to as the “social consensus reality” may be very different from “clarity” in an altered state. Indeed, there are those who feel that the true clarity occurs in certain drug-induced states, particularly certain LSD-related states, when the “veil of illusion” is cast aside, and the universe is truly revealed (Grinspoon and Bakalar, 1979). What is confusion to one person may have life-changing meaning to another. We also know how little of our brain is really necessary to maintaining a meaningful form of consciousness, and that a surprisingly large fraction of it can be lost without devastating changes.

It should also be emphasized that the glutamate theory is not a “simple chemical explanation.” The brain is clearly extremely complex with a very high level of interactivity and redundancy, and our understanding of its mysteries is in its infancy. The theory does explain how experiences arise in a “dysfunctional” brain, if we consider a brain confused and disorganized by ketamine to be dysfunctional. One doctor’s delirium is another’s NDE, but most people would agree that falling asleep involves a loss of consciousness, and yet an altered form of consciousness can be very rapidly resynthesized in the form of dreaming. Clearly, there are many forms of consciousness, and the point at which Fenwick and I most clearly diverge in our views is the implication in his argument that there can be only one form of consciousness, in a light-bulb-on/light-bulb-off model, which is based on the medical model of a linear continuum between coma, stupor, clouding, and full consciousness. Certainly a particular level of cortical activity and organization is required to sustain one type of consciousness, the social consensus reality, but this is surely only one type among many. The study of altered states of consciousness is a rich field that includes many states of mind arising from a diversity of cerebral events, many of which are different from the normal one, and some of which may involve organic pathology.

That general terms will no longer suffice in this area is illustrated by recent findings using brain imaging techniques such as positron emission tomography (PET). The injection of ketamine does not simply result in “dysfunction” or general NMDA receptor blockade. Vollenweider (1994) has demonstrated, using PET, that ketamine causes a cortical-subcortical imbalance of sensory information processing. There is a sensory overload of the frontal cortex resulting in a hy-
permetabolic pattern. This is a specific dysfunction linked to a specific altered state of consciousness. An aim of the study was to explore "the complex inter-relationships between cerebral metabolic changes and psychological changes." It is not unreasonable to assume that there will be specific forms of "dysfunction" responsible for the NDE.

There is no reason why memory of an NDE should present any difficulty for a neurochemical explanation. We remember our dreams without remembering falling asleep, and we remember some parts of altered states produced by drugs but not others. The assumption that we need a normally functioning brain to form a memory would not appear to be supported by most of the evidence. Some persons are very confused on waking, or will even sleepwalk, and yet they can describe their dreams in detail. Even more interesting is the condition known as night terrors (World Health Organization, 1992). This is distinctly different from nightmares. The person wakes from stage 4 sleep (deep sleep), in which brain electrical activity is very simple, with a loud panicky scream and appears confused and disoriented for several minutes. Nevertheless, these persons are able to remember key fragments of dreams that have a particular nature. The most common is a simple dream of entrapment of some kind. These persons explain that they screamed because they developed a sudden self-awareness of having been locked into a place from which there is no escape. Electroencephalography confirms that these are not nightmares, as they do not arise during rapid eye movement sleep, and occur in the first few hours of the night, which is dominated by deep sleep, as distinct from dreams, which are more common in the latter half of the night (Kales, 1987; Lask, 1988). Even more interesting is that this condition, which would appear to be due to an abnormality in the mechanism of sleep, responds to psychotherapy (Kales, 1987; Lask, 1988). Thus no special pleading is required to explain memory in persons who have abnormally functioning brains.

It is also interesting to consider the head injury NDE described by Lilly, who sustained a serious head injury when he collided with the truck, and had an NDE that appeared to last for several weeks. The NDE as described suggests a continuation of the previous experiences with ketamine, rather than a fundamentally different state.

It is possible that in some cases there is little memory for events around the time of a head injury precisely because a dissociative experience has "removed" the person from those events to participate in an inner drama instead. That is, there is a clear memory for an NDE but none for surrounding events, because the person's experi-
ence was of an NDE. The person with night terrors may remember the dream, but not screaming. All they know of the latter may be the comments of those they live with and a sore throat.

It is noted that medial temporal seizures are associated with fear or extreme fear. However, I did not say that NDEs are medial temporal seizures, nor that ketamine causes medial temporal seizures. What I suggested was that NDEs involve abnormal electrical activity, but this could be of a distinctly different character from these seizures. PET studies with drugs have demonstrated some very complex loops and interaction patterns in the brain. It is also true that some NDEs are associated with panic and negative affect, but this variety less commonly comes to light for the reasons previously discussed.

**Response to Igor Kungurtsev**

I had suggested Igor Kungurtsev as a commentator on my paper because he has carried out some very interesting work using ketamine to aid "death-rebirth" psychotherapy. While I hoped that we would learn more of this promising avenue of treatment, his comments here were largely a series of personal beliefs that fall outside of what can be usefully debated in a scientific arena. The real reductionism is seen in the attempt to pull an obscuring, mystical curtain over the study of the NDE, which can advance knowledge no further. The excitement of this historical period lies in the study of the mind/brain interface with the new tools available to us, particularly new brain imaging tools, not in resorting to the myths of—to borrow a term from Kungurtsev—"archaic" religions that have not advanced our understanding for several thousand years. The value of neuroscientific studies that constantly produce many new facts, ideas, and medicines to improve the human condition would appear now to exceed that of ancient, stagnant speculations about reincarnation, which generate nothing new. All they have to say is that NDEs are evidence for the continuation of consciousness after the death of the body. True or false, there is no more that they can add.

The ketamine that Kungurtsev used in his transpersonal investigations was developed by scientists who believed in the laws of physics. While we owe much to real physics, metaphysics kept the world in suspended animation throughout a very long period of history now referred to as the Dark Ages. It was the proponents of everlasting life, chief amongst whom was the Pope, who would not look through
Galileo's telescope. In some respects, the new real-time neuroimaging techniques represent the new telescope, even more threatening to our sense of self-importance, meaning, and desire for control over biological reality than ever. Unfortunately, our psychological maturation as a species still lags far behind technological advance, as was the case in Galileo's day—less than an eye-blink away in evolutionary terms.

As Kungurtsev did not wish to accept the term "death" for the final end, which term would he like to use for the final end of life? This is a simply a matter of linguistics, and has no relevance to any matters of a philosophical, religious, or spiritual nature, unless, of course, he wishes to argue that no life ever ends and thus we do not need a word for its end. We will certainly need some sort of word for the permanent failure to function of the body, if we are to communicate meaningfully with each other. Dictionaries represent the consensus view on the meaning of a word. Those who do not accept the consensus will find their communication with the rest of us increasingly impaired.

I would like to end these comments with a quote from Albert Einstein, a scientist who has had a far greater impact to date on our lives than have parapsychologists:

The fairest thing we can experience is the mysterious . . . . It was the experience of mystery—even if mixed with fear—that engendered religion. A knowledge of the existence of something we cannot penetrate, of the manifestations of the profoundest reason and the most radiant beauty, which are only accessible to our reason in their most elementary forms—it is this knowledge and this emotion that constitute the truly religious attitude; in this sense, and in this alone, I am a deeply religious man. I cannot conceive of a God who has a will of the type of which we are conscious in ourselves. An individual who should survive his physical death is also beyond my comprehension, nor do I wish it otherwise; such notions are for the fears or absurd egoism of feeble souls. Enough for me the inkling of the marvelous structure of reality. (1935, p. 5)

Response to Melvin Morse

Melvin Morse again raised the issue of the evolutionary advantage of the NDE. This matter was dealt with both in my original paper and above. In brief, the NDE results from protective forces against brain damage and also has psychological advantages in preventing
the organism from being overwhelmed with anxiety. The psychological advantage may be even greater where the forces of the unconscious are harnessed to give the person a strong message to go back, and that it is not their time. As those who have NDEs do not in fact die, the evolutionary advantage could be tremendous. Unfortunately, we do not know if persons who do actually die have an NDE.

The literature describing the effects of ketamine in the same terms as the NDE is perhaps not as weak as Morse described it. In fact, ketamine has been administered many times in clinical anesthetic studies. I did not cite this large quantity of anesthetic literature, primarily for practical reasons: my paper already had many references. I wished to present a hypothesis for discussion, not a definitive review of the effects of ketamine, as I cited several excellent reviews to which the interested reader may turn. Those accounts of the effects of ketamine I have presented here are amongst the most interesting and graphic, but there are many more scientific accounts in peer-reviewed journals. A computer search on "ketamine" will produce a vast quantity of formal research, much of it by anesthetists publishing methods of preventing the patient from having an NDE. Such a search would probably not reveal some of the more intriguing references cited here, which is an even better reason for bringing them to the light of day. Lester Grinspoon and James Bakalar (1979) commenced their book with a quote from Alfred North Whitehead, which could be considered here, and which is certainly believed by the near-death researchers Morse mentioned, such as Raymond Moody and Kenneth Ring:

The rejection of any source of evidence is always treason to that ultimate rationalism which urges forward science and philosophy alike. (p. vii)

With respect to quoting speculations by Ronald Siegel, this was done more to credit Siegel's contribution to aspects of the hypothesis than as evidence, which would indeed be inappropriate.

Response to Stuart Twemlow and Glen Gabbard

Twemlow and Gabbard offered valuable insights upon the psychodynamic and sociocultural aspects of the NDE, areas of considerable interest and, where the psychodynamic aspects are concerned, possible future therapeutic promise.
On the philosophical/religious issue again, I do regret making these comments about mind/brain dualism. The response has fully confirmed that the paradigms should not be confused. Most of the commentators have spent much space on these few, preliminary paragraphs, and very little upon the lengthy neuroscientific discussion, which is where the new ideas, possibility of experiments, and new avenues in psychotherapy lie. Clearly, I should not have discussed the paradigms on the same stage at all, not even to the extent of a few paragraphs, as this has served as a massive distraction at the expense of a proper consideration of the neuroscience itself.

That more mundane accounts could logically be expected from a state with a neurobiological origin is true because there is then no absolute requirement for an experience with religious/spiritual import, as there would be if the NDE had a religious/spiritual explanation. However, I had no intention to exclude explanations based on intrapsychic and sociocultural factors by my use of the term “neurobiological.” I completely adhere to the view of Twemlow and Gabbard that intrapsychic factors and cultural factors are important in generating NDEs.

Response to Antonio Bianchi

Antonio Bianchi has provided an interesting commentary and discussion, with much valuable information and new ideas. However, the ketamine doses he quoted were very much lower than those generally used to alter consciousness. His text stated that 1 to 2 milligrams intravenously or 3 to 5 milligrams intramuscularly of ketamine induces a trance-like state. These figures are not in accordance with those in the published literature. In most cases, it is unlikely that less than 20 milligrams intravenously of the Parke-Davis product Ketalar would produce a trance-like state. Bianchi cited the book by Moore and Alltounian (1978). These authors clearly stated their doses as 50-75 milligrams of ketamine intramuscularly.

That the effects of ketamine, like all drugs, can be influenced to some extent by set and setting is a matter that has already been discussed in relation to Strassman’s comments. This does not mean that different drugs will have the same effect in identical set and settings, however. LSD and ketamine are both likely to produce unpleasant results when given in hospital environments without adequate preparation of administrator and subject. However, the quality
of that unpleasantness will be very different, reflecting the individual character of the two drugs. The same can be said of DMT.

With respect to current interest in the use of ibogaine to treat addictions, ketamine has also been used for this purpose with an excellent success rate, and a much superior safety record (Krupitsky, Grinenko, Berkaliev, Paley, Tetrov, Mushkov, and Borodkin, 1992; Krupitsky, Grinenko, Karandashova, Berkaliev, Moshkov, and Borodkin, 1990; Krupitsky, Paley, Berkaliev, Ivanov, Dubrovina, Kohanzarova, Dunaevsky, Rhizankova, and Grinenko, 1993). The use of ketamine in the treatment of alcoholism is an area of great future promise.

That ibogaine binds to NMDA receptors is also of great interest from an ethnobotanical perspective. All of the powerful mind-altering substances we have discovered appear to have analogues in plants. Ketamine and PCP were the exceptions to this rule, perceived as "highly artificial" compounds. The discovery that ibogaine acts as a PCP/ketamine analog removes this exception, and suggests that the relationship between mind/brain and plant substances is truly comprehensive.

Postscript

I am no longer as opposed to spiritual explanations of near-death phenomena as my article and this response to the commentaries on it would appear to suggest. Over the past two years (it has been quite some time since I first drafted the article) I have moved more toward the views put forward by John Lilly and Stanislav Grof: namely, that drugs and psychological disciplines such as meditation and yoga my render certain "states" more accessible. The complication then becomes defining just what we mean by "states" and where they are located, if indeed location is an appropriate term at all. But the apparent emphasis on matter over nonmatter contained within this article no longer accurately represents my attitudes.

My forthcoming book Ketamine will consider mystical issues from quite a different perspective, and will give a much stronger voice to those who see drugs as just another door to a space, and not as actually producing that space. After 12 years of studying ketamine, I now believe that there most definitely is a soul that is independent of experience. It exists when we begin, and may persist when we
end. Ketamine is a door to a place we cannot normally get to; it is definitely not evidence that such a place does not exist.

I regret my past emphasis on the overriding importance of theories of matter as they stood in the late 1980s. Ketamine suggests that we still have much to learn.

References


"A refreshing and stimulating look at a subject that has been trampled by hype and innuendo....probing and insightful questions posed to a multidisciplinary panel of experts unmask the veiled secrets of the NDE as never before."

—Michael B. Sabom, M.D., Author, Recollections of Death: A Medical Investigation

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