Anesthesia - the "other side" of consciousness

(The following excerpted from "Greatest Inventions of the past 2000 years" edited by John Brockman, Simon and Schuster)

Have you ever had surgery? If so, either a) part of your body was temporarily "deadened" by "local" anesthesia, or b) you "went to sleep" with general anesthesia. Can you imagine having surgery, or needing surgery, or even possibly needing surgery without the prospect of anesthesia? And beyond the agony-sparing factor is an extra added feature Eunderstanding the mechanism of anesthesia is our best path to understanding consciousness.

Anesthesia grew from humble beginnings. Inca shamans performing trephinations (drilling holes in patients' skulls to let out evil humors) chewed coca leaves and spat into the wound, effecting local anesthesia. The systemic effects of cocaine were studied by Sigmund Freud, but cocaine's use as a local anesthetic in surgery is credited to Austrian ophthalmologist Karl Koller who in 1884 used liquid cocaine to temporarily numb the eye. Since then dozens of local anesthetic compounds have been developed and utilized in liquid solution to temporarily block nerve conduction from peripheral nerves and/or spinal cord. The local anesthetic molecules bind specifically on sodium channel proteins in axonal membranes of neurons near the injection site, with essentially no effects on the brain.

On the other hand general anesthetic molecules are gases which do act on the brain in a remarkable fashion Ethe phenomenon of consciousness is erased completely while other brain activities continue.

General anesthesia by inhalation developed in the 1840's, involving two gases used previously as intoxicants. Soporific effects of diethyl ether ("sweet vitriol") had been known since the 14th century, and nitrous oxide ("laughing gas") was synthesized by Joseph Priestley in 1772. In 1842 Crawford Long, a Georgia physician with apparent personal knowledge of "ether frolics" successfully administered diethyl ether to James W. Venable for removal of a neck tumor. However Long's success was not widely recognized, and it fell to dentist Horace Wells to publicly demonstrate the use of inhaled nitrous oxide for tooth extraction at the Massachusetts General Hospital in 1844. Although Wells had apparently used the technique previously with complete success, during the public demonstration the gas-containing bag was removed too soon and the patient cried out in pain. Wells was denounced as a fake, however two years later in 1846 another dentist William T.G. Morton returned to the "Mass General" and successfully used diethyl ether on patient William Abbott. Morton used the term "letheon" for his then-secret gas, but was persuaded by Boston physician/anatomist Oliver Wendell Holmes (father of the Supreme Court Justice) to use the term anesthesia.

Figure 1. *William T.G. Morton administering anesthesia to William Abbott at Massachussetts General Hospital in 1846.*

Although its use became increasingly popular, general anesthesia remained an inexact art with frequent deaths due to overdose and effects on breathing until after World War II. Hard lessons were learned following the attack on Pearl Harbor □Eanesthetic doses easily tolerated by healthy patients had tragic consequences on those in shock due to blood loss. Advent of the endotracheal tube (allowing easy inhalation/exhalation and protection of the lungs from stomach contents), anesthesia gas machines, safer anesthetic drugs and direct monitoring of heart, lungs, kidneys and other organ systems have made modern anesthesia extremely safe. However one mystery remains. Exactly how do anesthetic gases work? The answer may well illuminate the grand mystery of consciousness.

The following is a commentary on two papers by E.Roy John in an upcoming issue of Consciousness and Cognition

Anesthesia: the "other side□Eof consciousness

(Commentary on the papers of E. Roy John and colleagues)

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I. Monitoring depth of anesthesia

The two papers by E. Roy John and colleagues in this issue illustrate that general anesthesia is a direct avenue toward understanding not only the neural correlate, but also the molecular mechanisms of consciousness. Unlike normal sleep, anesthetized patients generally are insensitive to stimuli of any

kind, do not dream, have no sense of the passage of time, and generally awake with their consciousness completely unaffected (after drug effects have worn off) with no memory of events during the surgical procedure.

There are, however, extremely rare exceptions, and the incidence of intra-operative awareness and recall is a significant problem (e.g. Heier & Steen, 1996a). Many such cases are attributable to some form of "pilot error" in which inadequate amounts of anesthetic are administered for various reasons (e.g. vaporizers running dry, patients having unappreciated tolerance to anesthetic drugs etc.), or extreme situations (e.g. trauma with massive blood loss, fetal distress in Caesarian section) in which assuredly adequate anesthetic concentrations cannot be safely administered. However there are also some extremely rare cases of "recall" of intraoperative events in which the anesthetic seems in retrospect to have been perfectly well administered. Furthermore several studies show that implicit learning can occur under anesthesia (e.g.Ghoneim & Block, 1997) and some pundits suggest that patients may routinely be aware but simply don't remember (amnesia not anesthesia; Bonebakker et al., 1996). However anesthetists follow changes in visceral signs (heart rate, blood pressure, lacrimation, muscle tone etc.) which occur well before conscious awareness, and then "deepen" the anesthetic accordingly so that awareness is avoided. Consequently it seems very unlikely that anesthetized patients are routinely aware without some indication of changes in these vital signs. Nevertheless we can't know for certain simply because we can't directly measure consciousness, nor do we really understand what consciousness actually *is*. Compounding this problem is the fact that some researchers in the field operationally define anesthesia as merely 1) immobility in response to noxious stimuli, and 2) amnesia (Eger et al., 1996). While this is convenient for experimental purposes in both human subjects and animals it is an unfortunate "post-modern deconstruction" of the concept of anesthesia, and abdicates a unique opportunity to study consciousness.

Table 1. Techniques that have been used in the assessment of depth of anesthesia (Drummond, 2000)

Craniofacial electromyography

Respiratory sinus arrythmia

Heart rate variability

EEG derivatives

  Spectral edge frequency

  Median power frequency

  Power band ratios

Evoked responses

  P300

  Middle latency evoked response

Auditory steady state response (ASSR)

Coherent frequency of the ASSR

Contingent negative variation

Lower esophageal contractility

Electroretinography

Although consciousness cannot be directly measured or observed, various EEG and other techniques have been used to monitor the brain during surgical anesthesia in an effort to follow a neural correlate of consciousness and detect and avoid intra-operative awareness (Table 1; c.f. Heier & Steen, 1996b; Drummond, 2000). Several devices have utilized EEG data subject to Fourier transform so that EEG activity is displayed as a spectrum of power over various frequencies. This technique compresses the data for quick perusal, and in general shows that as patients become anesthetized and lose consciousness, EEG power shifts to lower frequencies. The frequency at the 95th percentile of EEG power (the "spectral edge□E has been used as a single parameter for anesthetic depth with some success. A current clinical technique is "bispectral analysis - BIS□Ewhich examines synchrony among different brain regions and other factors and produces a single parameter (the "bispectral index□E which purportedly indicates a more precise anesthetic "depth□Ethan spectral edge (Rampil, 1998; Todd, 1998). The precise derivation of the bispectral index has been kept proprietary, however despite massive promotion and media manipulation (Katz, 1999; Todd, 1999), bispectral analysis has proven to be faulty and only marginally better than spectral edge and other previous techniques (Drummond, 2000). Another technique, mid-latency auditory evoked potentials are more reliable (Thornton and Sharpe, 1998), but cumbersome and not widely available. An expert in brain electrophysiology, Professor E. Roy John has turned to this problem and developed the QEEG technique described in the first of his two papers.

II. Invariant reversible quantified EEG effects of anesthetics

The first paper by John and colleagues describes a study in which EEG data were recorded from 176 patients undergoing general anesthesia with a variety of different anesthetic techniques: 1) "purely□Egas inhalation (isoflurane, desflurane and sevoflurane), 2) intravenous anesthesia with propofol infusion, and 3) nitrous oxide inhalation and intravenous narcotics. A set of quantified EEG measures were identified independent of anesthetic type which were followed during specifically designated periods: 1) consciousness prior to and during induction of anesthesia, 2) just after loss of consciousness, 3) stable anesthetic (unconscious) state prior to return of consciousness, and 4) just after return of consciousness.

Comparing data from anesthetized and conscious states identified a set of invariant changes which reverted after return of consciousness, and which represent a putative correlate of anesthetized unconsciousness. The changes were the same irrespective of the type of anesthetic technique (unlike BIS in which the indicators of anesthesia vary among different anesthetic techniques and drugs). These

changes included an increase in power in all frequency bands with the exception of a decrease in gamma activity power, a marked anteriorization of power with increased coupling of pre-frontal and frontal hemispheric regions, and uncoupling between anterior and posterior regions, and between homologous regions of the two hemispheres. Anatomical correlations point to anterior brain regions as the sites of greatest changes, and presumably most direct involvement in consciousness. These findings are consistent with models proposing key roles for reticular and thalamic projections (Jasper & Komaya, 1968; Baars, 1988) and gamma frequency activity ("coherent 40 Hz□E e.g. Singer et al., 1990; Crick and Koch, 1990). Professor John and his team seem to have found a measurable neural correlate of consciousness by finding the neural correlate for the specific lack of consciousness. As a clinical tool the technique is independent of the particular anesthetic used (unlike the BIS index which varies with different anesthetics) and is able to monitor depth of anesthesia and potentially help reduce or eliminate intra-operative conscious awareness and recall. Indeed a new device (the "Patient State Analyzer□E.based on this work is being introduced into clinical anesthetic practice.

III. E. R. John's "quantum-like□Efield theory of consciousness

John's second paper, "A field theory of consciousness□Egoes further to consider how these findings reflect on what consciousness actually *is*. The most salient is the observation of "zero phase lag coherence□Eacross widely distributed areas of the brain during consciousness. As Professor John points out this implies that connectionist models of coherent synchrony (and consciousness) must be incorrect as each synaptic connection imparts a finite delay (phase lag). Another conventional explanation, that underlying pacemaker cells project to and synchronize cortical neurons as a conductor might synchronize members of an orchestra also won't work. As John points out this would require that the pacemaker cells know *a priori* precisely which neurons are to be activated. What *is* the explanation?

Simultaneity implies an instantaneous process, and recent clinical evidence supports quantum mechanisms in brain information propagation (Weinand, 2001). John describes a "quantum-like□Efield permeating the brain and correlating with, or perhaps comprising consciousness.

Field effects in the brain have been proposed previously, perhaps initially by Wolfgang Kohler in the early 20th century. Benjamin Libet (1994; 1996) has suggested a "Conscious mental field" produced by brain activity but phenomenologically distinct from brain activity. He describes the field as *not* being electromagnetic, but doesn't specify what type of physical field it could be. Pockett (2000) has identified consciousness with "certain spatiotemporal configurations□Eof the brain's electromagnetic field, suggesting that only particular electromagnetic configurations are conscious, but not specifying what those configurations might be. Pockett also details compelling evidence for a field effect related to consciousness, and John's zero phase lag data adds to this evidence. John's proposal also includes the notion that the consciousness field is discontinuous, parsed into epochs of roughly several hundred milliseconds. But what is the nature of the field, and what exactly is the meaning of "quantum-like□E

"Quantum-like□Erefers to similarities between brain functions and certain aspects of quantum theory which describes the bizarre properties of matter and energy at near-atomic scales. These properties

include quantum coherence (individual particles yield identity to a collective, unifying wave function, e.g. Bose-Einstein condensates), non-locality (spatially separated particle states are nonetheless connected, or "entangled□E, quantum superposition (particles exist in two or more states or locations simultaneously) and "collapse of the wave function□E(superpositioned particles reduce, or collapse to distinct, definite states or locations—a mechanism utilized in quantum computers). These properties have prompted comparisons to certain aspects of consciousness: quantum coherence and Bose-Einstein condensation as the "binding□E or unity of consciousness (e.g. Marshall, 1989), non-local entanglement as associative memory (e.g. Woolf & Hameroff, 2001), and quantum computation as the transition from non-conscious/pre-conscious processes to consciousness.

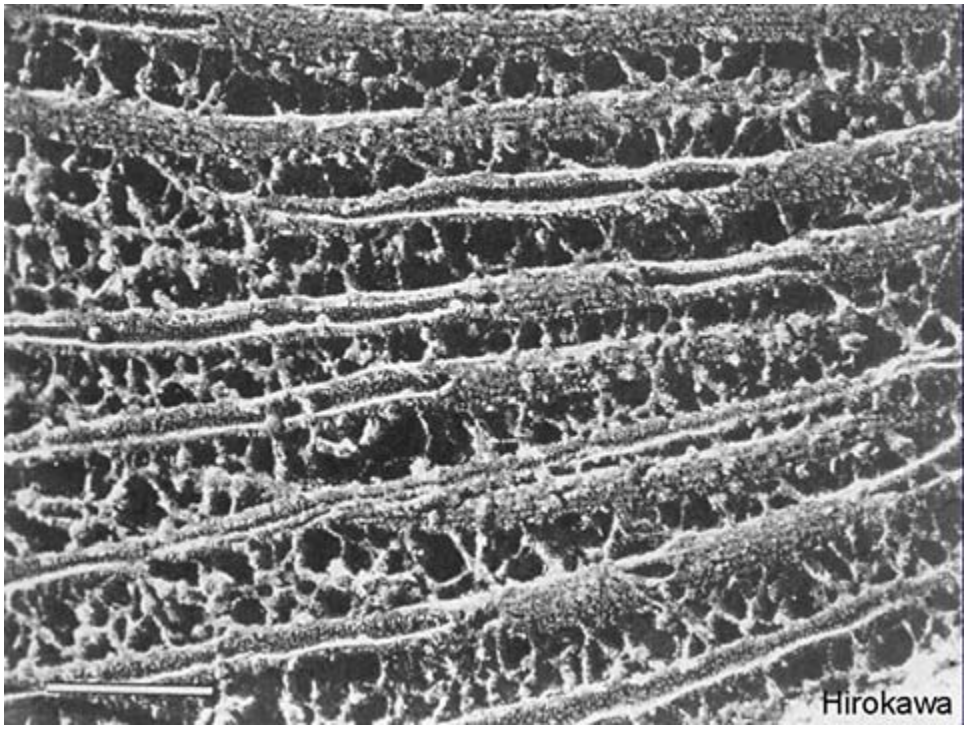

Figure 1. *The neuronal cytoskeleton. Immunoelectron micrograph of dendritic microtubules interconnected by dendrite-specific MAPs. Some microtubules have been sheared, revealing internal hollow core. The granular "corn-cob" surface of microtubules is barely evident to close inspection. Scale bar, lower left: 100 nanometers. With permission from Hirokawa, 1991.*

In quantum computation, elementary information may exist in discrete bit states, e.g. 1 or 0 as in classical computers, as well as in quantum superposition ("qubits□E of *both* states i.e. 1 AND 0. While in superposition qubits communicate and compute in a highly efficient manner, then reduce or collapse to classical states as output. Quantum computers ffer enormous potential advantages for certain applications, and prototype devices have been constructed, promising a revolutionary technology. Perhaps quantum computation evolved in biological systems as the most efficient form of information technology.

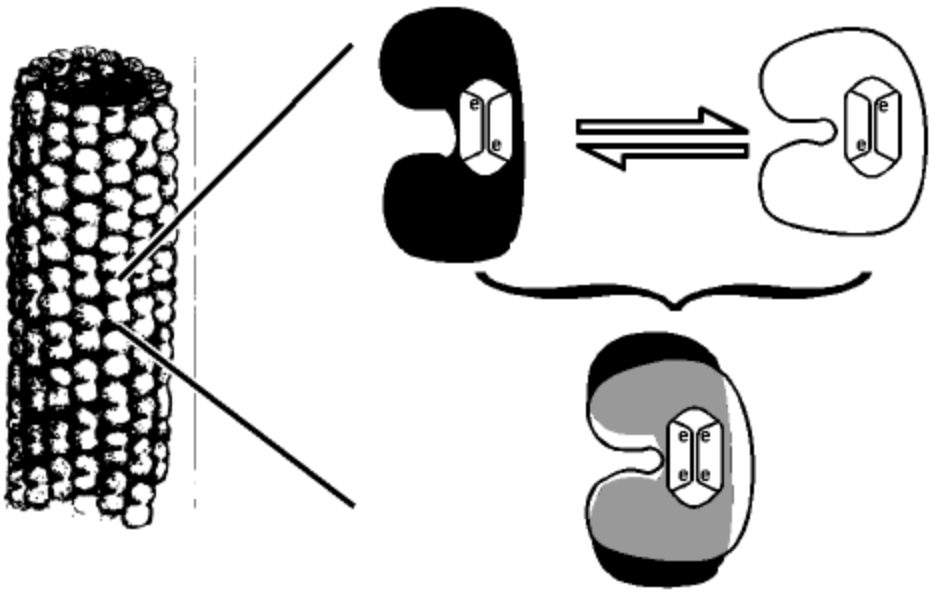

Figure 2. *Left: Microtubule (MT) structure: a hollow tube of 25 nanometers diameter, consisting of 13 columns of tubulin dimers arranged in a skewed hexagonal lattice (Penrose, 1994). Right (top): Each tubulin molecule may switch between two (or more) conformations, coupled to London forces in a hydrophobic pocket. Right (bottom): Each tubulin can also exist in quantum superposition of both conformational states (Figure 1a, c.f. Hameroff and Penrose, 1996b).*

Penrose (1989; 1994) correlated the multiple possibilities of quantum superposition with multiple sub-conscious, or pre-conscious possibilities "collapsing□Eto distinct choices or perceptions (c.f. Stapp, 1993). The Penrose-Hameroff "Orch OR□Emodel portrays consciousness as a form of quantum computation in cytoskeletal microtubules within neuronal cytoplasmic interiors. Microtubule subunit proteins ("tubulins□E are suggested to function as qubits, able to exist in quantum superposition of two or more conformations (Figures 1 and 2). Following periods of pre-conscious quantum computation (e.g. on the order of tens to hundreds of milliseconds) the tubulin superpositions are suggested to reduce or collapse to classical output states which then govern neurophysiological events (e.g. Penrose & Hameroff, 1995; Hameroff & Penrose, 1996a; 1996b; Hameroff, 1998a). The reduction or "self-collapse□Ein the Orch OR model is suggested to be a "conscious moment□E linked to a quantum gravity mechanism proposed by Penrose which ties the process to fundamental spacetime geometry, enabling a pan-protopsychist approach to the "hard problem□E of subjective experience (Chalmers, 1996). Woolf (1997) has shown how classical synaptic activity (e.g. acetylcholine binding to post-synaptic receptors) can initiate a quantum state within neuronal interiors by decoupling and isolating the cytoskeleton from membrane and external influences. Thus quantum state reductions in microtubules are specific events which are compatible with known neurophysiology, may correspond with discrete cognitive epochs as shown in John's study, and from a philosophical perspective may be equivalent to Whitehead's "occasions of experience□E(Shimony, 1993).

Quantum models have potential explanatory value for the enigmatic features of consciousness, but face at least two apparent obstacles: 1) the apparent likelihood of rapid "decoherence□E(loss of quantum state) due to environmental thermal interactions in the seemingly-too-warm brain (Tegmark 2000; Seife, 2000), and 2) the question of how a quantum state or field which might conceivably be isolated *within*

neurons might extend across membranes and anatomical regions to approach “brain-wide□Eproportions. Accordingly, Professor John and others have embraced the compromise of “quantum-like□Eprocesses, sensibly unwilling to “bite the bullet□Eand commit to functional macroscopic quantum states in the brain milieu.

But I personally wouldn’t bet against such states. Quantum computing is far superior to classical computing in certain critical functions (e.g. Grover’s quantum search algorithm), and would be of extreme biological benefit for survival and adaptation. Billions of years of evolution may have solved the problems of decoherence and spatiotemporal spread. A number of mechanisms to prevent environmental decoherence have been suggested, specifically for quantum computation in microtubules. These include 1) coherent pumping of the environment, 2) screening due to counterion Debye double layers surrounding microtubules, 3) screening by actin gelation and ordered water, 4) quantum error correction, 5) topological effects of the microtubule cylindrical lattice. Recent calculations of protein decoherence times indicate quantum superpositions may indeed survive for neurophysiological time durations (Hagan et al, 2000), and brain imaging by “quantum coherence MRI□Eutilizes quantum couplings of proton spins in proteins and water to give a neuroanatomical correlate of consciousness (Richter et al, 2000; Rizi et al, 2000). This quantum coherence is an MRI-induced artifact, but shows that quantum coherence of some sort can indeed occur in the brain.

Regarding spatial extension of a quantum (or “quantum-like□E field throughout the brain, a possible solution may be gap junctions —window-like “electrical□Econnections between cells including neurons (e.g. Dermietzel & Spray, 1993). Gap junctions are more primitive and less numerous connections than chemical synapses, and occur between dendrites, axons, cell bodies and/or glial cells. Dendritic-dendritic gap junctions in particular have been implicated in the mediation of conscious processes (Pribram, 1991; Eccles, 1992). Cell interiors (cytoplasm) are continuous through gap junctions so that cells connected by gap junctions have actually one complex interior. Quantum states isolated in one cell interior may thus extend to neighboring cells by quantum tunneling across the 4 nanometer gap junction. Specific intracellular organelles have been discovered in dendrites, immediately adjacent to dendritic-dendritic gap junctions. These are layers of membrane covering a mitochondrion, and are called "dendritic lamellar bodies□E(de Zeeuw et al., 1995). The dendritic lamellar bodies are tethered to small cytoskeletal proteins anchored to microtubules, and it is suggested that the mitochondria within the bodies provide free electrons for tunneling, forming a tunneling diode pair or Josephson junction between cells (Figure 3). As few as three gap junction connections per cortical neuron (with perhaps thousands of chemical synapses) to neighboring neurons and glia which in turn have gap junction connections elsewhere may permit spread of cytoplasmic quantum states throughout significant regions of the brain, weaving a widespread syncytium whose unified interior hosts a unified quantum state or field (Hameroff & Penrose, 1996; Woolf & Hameroff, 2001).

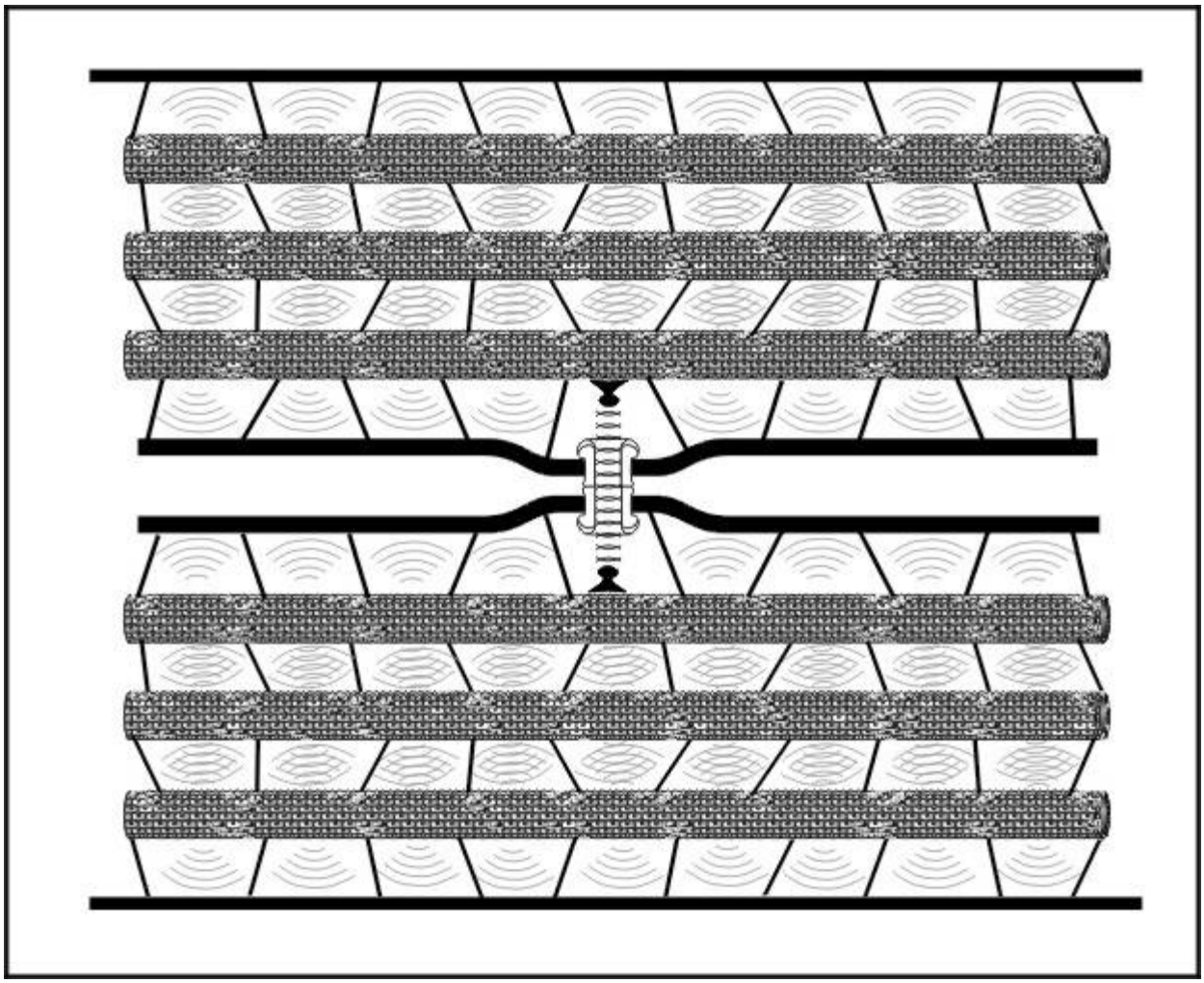

Figure 3. *Schematic representation of a gap junction connecting two dendrites in which microtubules are in quantum superposition/quantum computation "tuned□Eby interconnecting MAP proteins as suggested in the Penrose-Hameroff Orch OR model. On either side of the gap junction, dendritic lamellar bodies (DLBs) containing mitochondria may act as tunneling diodes to convey the quantum state between the dendrites.*

Kandel et al. (1991) remarked that neurons connected by gap junctions fire synchronously, behaving like "one giant neuron□E and professor John has suggested that gap junction-connected neurons ("hyper-neurons□E mediate zero phase lag coherence, and his "quantum-like□Efield. Dendritic lamellar bodies are associated with synchronously firing neurons (de Zeeuw et al., 1997) and several studies (Galaretta et al., 1999; Gibson et al., 1999; Velasquez & Carlen, 2000) implicate gap junction-connected interneurons in the mediation of coherent (□E0 Hz□E oscillations. These gap junction-connected interneurons form "dual□Econnections (gap junctions *and* GABAergic chemical synapses) with pyramidal cells and other cortical neurons. GABA inhibition could quiet membrane activities, avoiding decoherence to enable quantum states in neuronal cytoplasmic interiors to develop and spread among many gap junction-linked cells across wide areas of the brain. Thus gap junction-connected coherent 40 Hz neurons may support a widespread quantum-like field, or actual quantum field.

IV. What do anesthetics do to erase consciousness?

What else can we learn about consciousness from the phenomenon of anesthesia? An obvious route is to examine how anesthetics act at the molecular level.

Most general anesthetics are inhaled gas molecules which travel through the lungs and blood to the brain. Barely soluble in water/blood, all gas anesthetics are highly soluble in a particular lipid-like environment akin to olive oil. It turns out the brain is loaded with such stuff, both in lipid membranes and tiny water-free ("hydrophobic") lipid-like pockets within certain brain proteins. Meyer and Overton showed in the late 19th century that the potency of gas anesthetics was directly proportional to this solubility for a wide range of compounds over many orders of magnitude of potency (the "Meyer-Overton correlation□E. The compounds ranged from halogenated hydrocarbons, ethers and the inert element xenon, the common denominator being solubility in the lipid-like environment due to the formation of a particular type of van der Waals force (Halsey, 1989). For most of this century it was believed that the anesthetics acted in lipid regions of neuronal membranes, however Nicholas Franks and William Lieb at Imperial College in London showed in a series of articles in the 1980's that anesthetics act primarily in the tiny hydrophobic pockets in several types of brain proteins (Franks and Lieb, 1982; 1984; 1985; 1994).

The critical proteins determined by Franks and Lieb are receptors for $GABA_A$, glycine, serotonin, and acetylcholine as well as others which may be less sensitive but more plentiful and/or directly involved in consciousness. This latter group includes G-proteins, gap junction proteins and cytoskeletal proteins such as tubulin. The anesthetic binding is extremely weak and the pockets are only 1/50 of each protein's volume, so it's unclear why such seemingly minimal interactions should have such profound effects. Franks and Lieb suggested the mere presence of one or two anesthetic molecules per pocket per protein prevented the protein from changing shape ("conformational change□E to do its job (e.g. ion channels opening and closing). However subsequent evidence showed that certain other gas molecules could occupy the same pockets (follow the Meyer-Overton correlation) and *not* cause anesthesia (and in fact cause excitation or convulsions; Fang et al, 1996). Anesthetic molecules just "being there" can't account for anesthesia. Some natural process critical to consciousness and perturbed by anesthetics must be happening in these hydrophobic pockets.

Anesthetic gases dissolve in hydrophobic pockets by extremely weak quantum mechanical van der Waals forces known as London dispersion forces (Halsey, 1989). These are instantaneous couplings

of electron clouds between two or more non-polar atoms or molecules□Emutually induced dipoles. In other words the electron clouds of two (or more) neighboring atoms or molecules (e.g. one from an amino acid of the protein pocket, and one from the anesthetic molecule) shift instantaneous electron locations to avoid electron repulsion and maximize attraction between electrons and positively charged nuclei. The weak binding accounts for easy reversibility—as the anesthetic gas flow is turned off, concentrations drop in the breathing circuit and blood, anesthetic molecules are gently sucked out of the pockets and the patient wakes up. But why does such weak binding cause anesthesia?

It turns out that in the absence of anesthetics, i.e. during consciousness, these same weak London forces occur in the same hydrophobic pockets among electron clouds of amino acids and act to govern normal protein movement and shape because the various relatively strong bonds in proteins cancel out (Voet & Voet, 1995). A logical conclusion is that anesthetic-induced London forces perturb normally occurring London forces in hydrophobic pockets of brain proteins which are necessary for protein conformational dynamics and consciousness (Hameroff, 1998b). Because the location of an electron is a quantum process (the location cannot be definite at any time, and in fact is apparently smeared out spatially like a wave) London forces are quantum mechanical. Thus the underpinnings of neuronal activities are quantum mechanical interactions. If these interactions are unified in a common wave function then a quantum field and sequence of quantum events may indeed comprise consciousness.

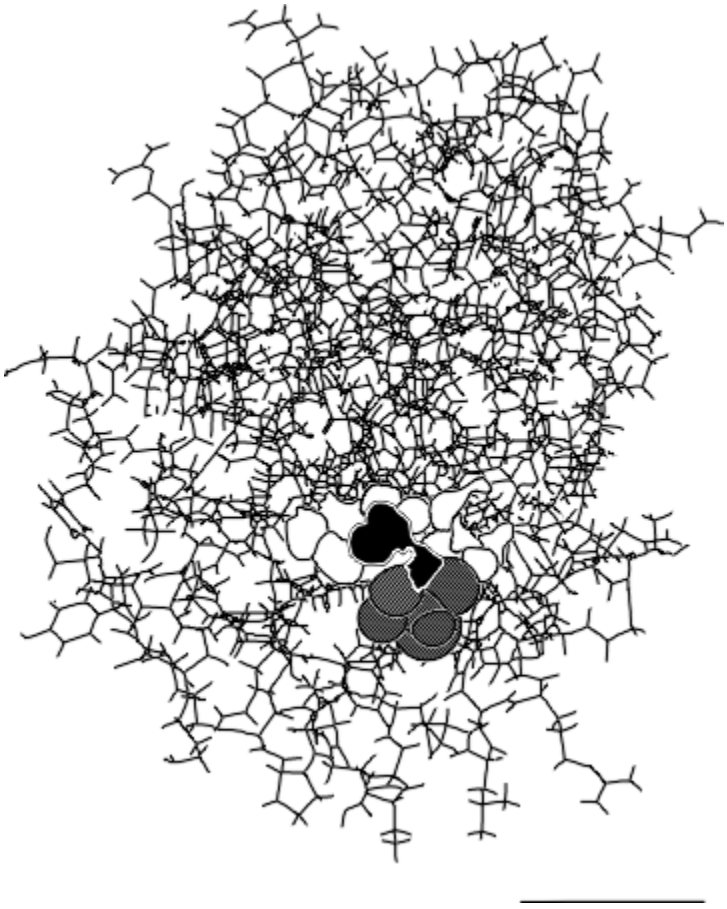

Figure 4. *Computer simulation of the anesthetic-sensitive enzyme papain with halothane (black)*

"docked" by energy minimization into its major hydrophobic pocket. Scale bar: 1 nanometer. (From Louria and Hameroff, 1996 with permission).

V. Conclusion

Research in anesthesiology may hold the key to understanding consciousness, and research into consciousness may help solve the problems of awareness and recall in anesthesiology.

The two papers by Professor John and colleagues are useful and illuminating, providing the following points for which the authors deserve our congratulations and gratitude:

- A well documented neural correlate of consciousness (by defining the neural correlate of the absence of consciousness
- A practical approach to monitoring anesthetic depth with the potential benefit of reduction or elimination of intraoperative awareness and recall
- A strong argument for a non-connectionist field defining consciousness in the brain
- Tacit support for quantum mechanisms related to consciousness

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