OPEN

Consciousness

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Understanding the mechanism of conscious experience—as well as its disruption due to physiological, pharmacological, and pathological causes—will be a major scientific achievement of wide-ranging importance.[1] There is arguably no medical specialty better positioned than anesthesiology to pursue a comprehensive explanatory framework. We possess the tools to manipulate the level, content, and behavioral expression of consciousness with a reproducible and controllable methodology (for nomenclature related to the science of consciousness, see Table 1). As a field, we should commit to addressing this challenge, making foundational scientific contributions, and solidifying our role as intellectual leaders whose scope extends beyond the operating room, critical care unit, and pain medicine clinic.

In the first issue of *Anesthesia & Analgesia*, published in August 1922, there was an article exploring the mechanism by which consciousness is suppressed during anesthesia. It posited "oxygen want" as the ultimate cause of cerebral failure.[2] A century later, we are still exploring the mechanisms of anesthetic-induced unconsciousness, but now with rigorous experimental methodology and investigations that range from large-scale brain networks to the subatomic level. As we celebrate this centennial event of *Anesthesia & Analgesia* and the International Anesthesia Research Society, it is also worth noting that 2022 is the 75th anniversary of a publication in *Science* by Henry K. Beecher, former chair of anesthesiology at the Massachusetts General Hospital, entitled "Anesthesia's Second Power: Probing the Mind."[3] This 1947 article was insightful and prescient, as Beecher described anesthetics as tools to dissect mental processes. Beecher's vision was decades ahead of its time, with the science of consciousness first formally developed in the mid-1990s and general anesthetics coming to the forefront in the 2000s as a method to understand the mechanisms of conscious experience and arousal states.[4–8] The science of consciousness was also part of an evolution in the investigation of anesthetic mechanisms, from biophysical and molecular approaches to a complementary systems neuroscience framework.[9,10]

There has been substantial progress in the past 2 decades, with a characterization of anesthetic effects on the neural regions, circuits, networks, and processes of relevance to both level and content of consciousness. But what does the future hold? Here, I discuss some key questions, of varying tractability, in the field of consciousness science as well as the potential role of anesthesiology and the related neurosciences to inform them.

WHAT IS THE BEST THEORETICAL FRAMEWORK TO EXPLAIN OR STUDY CONSCIOUSNESS?

Prominent theories of consciousness currently include global neuronal workspace theory,[11] integrated information theory,[12] higher order thought theory,[13] recurrent processing theory,[14] and orchestrated objective reduction theory[15] (a quantum physical approach; Table 2). Anesthetics can be and have been leveraged as important investigative tools to differentiate and assess these theories. However, more comprehensive and carefully controlled studies with general anesthetics—including ketamine and nitrous oxide, which have psychedelic properties at subanesthetic levels—can be designed to advance the field. This is critical because many seminal studies of anesthetic-induced unconsciousness can be viewed as consistent with multiple theoretical frameworks.

The role of the prefrontal cortex is a central point of differentiation across various theories of consciousness.[16,17] In higher order thought theory, the prefrontal cortex is the source of consciousness because it generates secondary or "meta" representations of primary sensory representations. In global neuronal workspace

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Table 1. Nomenclature of Relevance to the Science of Consciousness

General terminology

Easy versus hard problem of consciousness: "easy" problems of consciousness include understanding the neural basis of feature detection, integration, verbal report, etc. The so-called hard problem is the problem of experience; even if we understand everything about neural function, it is not clear how that would explain subjectivity, interiority, or point of view.

Wakefulness versus awareness: wakefulness refers to brain and behavioral arousals, which can occur even in pathological conditions of unconsciousness, whereas awareness refers to subjective experience. Note that the common clinical use of the term "awareness" in anesthesiology is shorthand for "undesired intraoperative awareness during intended general anesthesia, with explicit episodic recall of events."

Phenomenal versus access consciousness: phenomenal consciousness is proposed as a kind of "pure" subjective experience, whereas access consciousness is the broad availability of that experience to other cognitive processes (such as working memory or verbal report).

Connected versus disconnected consciousness: connected consciousness is the experience of environmental stimuli (such as the warmth of the sun), whereas disconnected consciousness is an endogenous experience (such as a dream state).

Level versus content of consciousness: level of consciousness includes distinctions such as alert versus somnolent versus anesthetized, whereas content of consciousness refers to particular qualitative aspects of experience (such as the proverbial "redness of a rose").

Behavioral versus covert consciousness: consciousness can be manifest behaviorally or, in states of cognitive-motor dissociation such as unresponsive wakefulness syndrome, can be obscured.

Methodological terminology

Report versus no-report paradigms: traditionally, studies of consciousness required a verbal or nonverbal "report" to signal perception. However, reporting might engage wider neural systems (ie, involving access versus phenomenal consciousness). Thus, emerging no-report paradigms try to detect perception without the need for volitional behavior that could confound the neural correlates of consciousness proper.

Connectivity versus complexity: connectivity and complexity are brain activity measures that represent surrogates of integration and differentiation, respectively. Integration (the unity of consciousness or neural binding of information) and differentiation (the diversity of experience or neural signals) are 2 key experiential and neurobiological dimensions of consciousness. Connectivity can be structural (the physical highways) or functional (the traffic along those highways). Complexity (eg, measured via the Lempel-Ziv algorithm) is intended to reflect the diversity or predictability of a signal. Deintegration, dedifferentiation, or both, are mechanisms by which consciousness can be disrupted, for example, during general anesthesia.

Table 2. Theories of Consciousness

Theory	Source of consciousness	Proposed neural mechanisms	Measurable neural correlates	Anesthetic effects
Global neuronal workspace[11]	Any information, initially encoded in 1 or several specialized cortical processors, whose content is globally broadcast to other cortical processors	Sudden ignition of a large-scale brain network of high-level cortical areas, linked by long-distance reentrant loops	Late (~300 ms) global ignition of distant areas, global information sharing, and other markers of long-distance information sharing across the workspace network	Reverberant connectivity and activity between nodes of the workspace are disrupted during anesthesia, including directed connectivity from prefrontal to more posterior cortices
Integrated information[12]	Information that is both integrated and differentiated, and which cannot be decomposed into causally independent parts	A confluence of posterior sensory and association cortices that represent a "hot zone" of neural processing	Surrogates of information integration and differentiation such as ϕ or the perturbational complexity index	Integration and differentiation are suppressed by general anesthetics, leading to a reduction in the repertoire of possible states; surrogates of ϕ are reduced during anesthesia
Higher order thought[13]	A first-order representation X that enters into a second-order, metacognitive representation (eg, the representation of a self currently seeing X)	Neural circuits in the prefrontal cortex that meta-represent information arising from other areas	Not determined	Not formally tested but activity of anterior prefrontal regions and other areas involved in higher order metacognitive representations could be suppressed during anesthesia via entrained oscillations or metabolic suppression
Recurrent processing[14]	Any neural code that is shaped by recurrent loops from higher order to lower order areas and back	Feedback connections in sensory pathways	Top-down signals reaching back to sensory areas due to recurrent loops	Top-down, recurrent processing within sensory cortex (specifically demonstrated for visual cortex) is selectively suppressed during anesthesia
Orchestrated objective reduction[15]	Orchestrated quantum computations and the collapse of superposed states	Brain-wide network of cytoskeletal elements (specifically, microtubules) that forms the biological substrate for quantum processes	Not determined, but theory predicts that signatures of quantum vibrations in networks of microtubules could be manifest in classical neurophysiology	Effects unknown during anesthesia but experimental models demonstrate the effects of anesthetics on subatomic particles and quantum processes; van der Waals dipole coupling can also be disrupted

Among many explanatory frameworks, these 5 theories are among the most widely debated and have been, or can be, informed by experiments involving general anesthesia. Note that extant data or analyses of anesthetic-induced unconsciousness cannot unambiguously differentiate or adjudicate among the theories. Modified with permission from Mashour et al.[11]

theory, the prefrontal cortex is the site of ignition that activates a recurrent network across anterior and posterior cortices, which helps sensory representations to be sustained, amplified, and made available to various cognitive processors that collectively contribute to conscious processing. In integrated information theory and related approaches, the prefrontal cortex is considered relevant to postperceptual cognition but not necessarily to experience itself. Studies of general anesthesia have already informed this controversy, but the field can be advanced by causal manipulation and careful analysis of neuronal ensembles and macroscopic oscillations in prefrontal cortex—with both temporal and spatial precision—during carefully titrated anesthetic administration and neurobehavioral assessment.

HOW DO WE RESTORE CONSCIOUSNESS IN PATHOLOGICAL CONDITIONS?

Although emergence from general anesthesia is variable and likely reflects intrinsic neural dynamics, it is rare to not recover.[18] By contrast, pathological conditions such as unresponsive wakefulness syndrome (formally known as the vegetative state) or minimally conscious state can persistently disrupt conscious experience. Although the pathways to pharmacological and pathological states of unconsciousness are distinct, there are shared neurobiological features. This is evidenced by the recent demonstration using neuroimaging that machine learning strategies based on anesthetic-induced unconsciousness can inform the classification of pathological states of unconsciousness.[19] Beyond diagnostic considerations, recent strategies focused on the reversal of general anesthesia through the manipulation of subcortical and cortical sites[20–34] (Table 3) can be modified and applied to disorders of consciousness. This represents an important contribution that anesthesiology can make to fields like neurology and neurorehabilitation.

HOW DO WE MEASURE NEURAL INFORMATION?

Investigations of consciousness and general anesthesia in the past decade have shifted to the level of information generation, processing, and transfer within complex networks.[35] But what is neural information and how do we measure it? Current studies use various and imperfect measures such as complexity or connectivity as surrogates for the differentiation and integration of neural information, respectively (Table 1). Although these approaches have advanced the field, they still do not address the fundamental question: what is the state of information during consciousness and anesthesia? Neuroimaging and neurophysiological studies suggest that incoming sensory information can reach primary sensory cortex and possibly be represented there.[36–38] Is this level of representation associated with fragments of experience or thoughts without a thinker?[39] Is information trapped in various perceptual and cognitive islands during general anesthesia? If so, how can we measure this informational content?

The integrated information theory of consciousness has a mathematical formalism on which it is based and a proposed measure (denoted by the Greek letter phi) for information integration that purports to reflect the capacity for consciousness.[40] However, this can only be applied to various simple model systems. There have been attempts to leverage the principles of this computation and adapt them for practical settings, such as high-density electroencephalogram recordings in humans undergoing general anesthesia.[41] However, we are far from understanding the neural code for consciousness and how those informational processes can be measured in real time and in the real world of the operating room or critical care unit.

CAN WE DEVELOP A BEHAVIOR-INDEPENDENT METRIC OF CONSCIOUSNESS?

In clinical anesthesiology, we have grappled with the problem of intraoperative awareness and the explicit episodic recall of surgical events in patients intended to be fully anesthetized.[42,43] This problem and related sequelae are more likely to occur with the use of neuromuscular blockers[44,45] because purposeful movement, the primary behavioral manifestation of consciousness, is suppressed. Such cognitive-motor dissociations can also occur in neuropathological conditions, independently of pharmacology, rendering patients covertly conscious.[46] However, the problem is much wider than these clinical situations because, ultimately, all attributions of consciousness in others are related to behavior.

You and I are privy to one and only one instance of subjectivity: our own. Otherwise, we make inferences and assumptions regarding consciousness that are behaviorally based. This generally works well in everyday life but not always in the operating room or critical care unit, where impaired behavioral expressions can lead to false conclusions of unconsciousness.[47] This problem also applies to species that cannot respond meaningfully using language. Additionally, 21st-century technology is turning the problem on its head: clinically, we have grappled with unresponsiveness being mistaken for unconsciousness, but now we must also grapple with the possibility of responsiveness being mistaken for consciousness. As machines become increasingly sophisticated in their behavioral interactions, at one point might we ask whether they have acquired consciousness?[48] And how will we answer this question when it does arise? To address the connections and dissociations between behavior and subjectivity, we need to understand the

Table 3. Neural Activation Studies in Animals That Involve the Reversal of Anesthesia or Acceleration of Passive Emergence

Brain site	Anesthetic	Stimulation technique	Species	Notes
Anterior nucleus gigantocellularis[20]	Isoflurane (1.25%–1.5%)	Pharmacological (bicuculline and gabazine) and optogenetic	Mouse	Hypoglycemic coma also reversed
Parabrachial nucleus[21–23]	Isoflurane (0.9%–1%), sevoflurane (1.2%–2.0% dose response), and propofol (48 mg/kg/h)	Electrical (60 μA for isoflurane study), chemogenetic (for propofol and sevoflurane studies), and optogenetic (for sevoflurane study)	Mouse (for isoflurane and sevoflurane studies) and rat (for propofol chemogenetic study)	Chemogenetic activation during propofol had a selective effect on passive recovery (versus induction)
Locus coeruleus[24]	Isoflurane (2.0%)	Chemogenetic	Rat	Passive recovery studied
Ventral tegmental area[25,26]	Isoflurane (0.9%) and propofol (plasma target 4.4 μg/mL)	Electrical (up to 120 μA) and optogenetic (dopaminergic neurons targeted)	Rat (for electrical stimulation study, isoflurane and propofol) and mice (for optogenetic study, isoflurane)	Systemically administered dopaminergic agonists also effective
Lateral hypothalamus, perifornical region[27]	Isoflurane (1.4% or 0.8%)	Optogenetic	Rat	Passive recovery studied; focus on orexinergic terminals in basal forebrain and locus coeruleus
Thalamus (nonprimate), central medial[28]	Sevoflurane (1.2%)	Pharmacological (nicotine)	Rat	Follow up study[29] infusing Kv1.2 potassium channel blocking antibody in central medial thalamus showed similar arousal effect during 1.2% sevoflurane or 3.6% desflurane
Thalamus (primate), centrolateral[30]; mediodorsal and intralaminar nuclei[31]	Isoflurane (0.8%–1.5% for centrolateral study) and propofol (0.17–0.33 mg/kg/min for centrolateral study and 0.14–0.23 mg/kg/min for mediodorsal and intralaminar studies)	Electrical (100–300 μA for centrolateral experiments) and 180-Hz bipolar stimulation (for mediodorsal and intralaminar experiments)	Monkey	Various cortical neurophysiologic markers of consciousness were restored with thalamic stimulation
Basal forebrain,[32] basal forebrain cholinergic neurons[33] (for studies of isoflurane and propofol)	Desflurane (4.6%), isoflurane (1.4%), and propofol (20 mg/kg, single dose)	Pharmacological (norepinephrine during desflurane) and chemogenetic/optogenetic (during isoflurane and propofol)	Rat (for pharmacologic stimulation, desflurane) and mice (for chemo/optogenetic stimulation, isoflurane and propofol)	For chemo/optogenetic experiments, induction and passive recovery were studied
Prefrontal cortex[34]	Sevoflurane (1.9%–2.4%)	Pharmacological (carbachol)	Rat	Carbachol in posterior parietal cortex was not effective in restoring wakefulness

Note that this list is not comprehensive and focuses primarily on experimental studies with specific manipulation of neural circuits or regions rather than systemic administration of drugs or other interventions to accelerate recovery from anesthesia.

principled determinants of consciousness and to measure them in a way that is independent of behavioral expression.[49]

WHAT HAPPENS TO CONSCIOUSNESS AROUND THE TIME OF DEATH?

The near-death experience has been reported since antiquity and was more formally described in the psychology literature of the 1970s. For the most part, the phenomenology of these experiences is culturally invariant. What is happening at this border of life and death, the known and unknown? It has been argued that a noncorporeal basis for consciousness is the only way humans could experience such vivid phenomenology, consistently described as "realer-than-real," in the setting of clinical death or coma.

These metaphysical questions seem far removed from the realm of anesthesiology, but they are not. First, prospective epidemiological studies published in highly regarded, peer-reviewed journals indicate that 9% to 18% of in-hospital cardiac arrest patients, who are often cared for by anesthesiologists, report near-death experiences.[50,51] Second, precipitous increases in the Bispectral Index around the time of death have been reported in dying patients in the operating room and critical care unit.[52,53] Third, analytical techniques used to characterize anesthetic state transitions have demonstrated, in highly controlled animal studies, that some neural correlates of consciousness surge just after experimental cardiac or respiratory arrest.[54,55] Characterizing the neurobiology of the dying brain and determining whether near-death brain states can sustain conscious experience will have wide-ranging implications from neuroscience to biomedical ethics to religion. Anesthesiologists are well positioned to study this both experimentally and clinically.

WHEN AND WHY DID CONSCIOUSNESS EVOLVE?

When consciousness emerged along the phylogenetic timeline has been a longstanding question. It was a focus of inquiry—as well as a source of intellectual distress—for Charles Darwin. Some still question whether consciousness emerged before *Homo sapiens*, while others question whether the emergence of consciousness conferred a specific selective advantage or whether it is merely epiphenomenal to more complex information processing in the brain. This is fundamental biology that needs to be clarified.[56] But how can we address this when we only have access to a cross section of living species rather than the evolutionary span of a phylogeny? We, in anesthesiology, have something to offer. First, it is important to note that general anesthesia is a biological phenomenon that occurs in a wide variety of organisms, from primates to plants to paramecia.[57] Thus, we have a unique tool to probe foundational interactions between an organism and its environment, with remarkably conserved anesthetic end points. For example, anesthetics impair rudimentary sensation and motility in single-cell organisms.[57] Can we use anesthetics to better understand how organisms evolved from detecting pH changes or chemical gradients to subjectivity?[58] As noted above, a principled and behavior-independent metric of consciousness will be needed.

This still leaves us wondering what neural structures or processes were required for the emergence of consciousness. Again, we in anesthesiology might have something to offer because, hundreds of millions of times a year across the world, we witness the emergence of consciousness from the oblivion of general anesthesia. Careful assessment of activity or interactivity of neural structures during emergence can elucidate the requirements for the core conscious experience. Such assessment has been formally proposed as a method for studying the neural machinery required for experience.[59] This is especially relevant because some studies and clinical observations suggest that recovery proceeds from caudal (more evolutionarily conserved) to rostral (more evolutionarily recent) areas of the brain.[60,61]

WHAT IS THE RELATIONSHIP BETWEEN CONSCIOUS EXPERIENCE AND THE PHYSICAL WORLD?

The relationship between the apparently "subjective" nature of experience and the apparently "objective" nature of the world is arguably the most fundamental question in the science of consciousness. At one level, the question was debated in philosophy through the frameworks of empiricism, in which experience is shaped by the world, and idealism, in which the world is shaped by experience. In neural terms, does the brain serve to process the environmental and visceral stimuli presented to it, or is the brain a closed system that generates information independently of what is "out there"? Furthermore, does conscious experience exist in physical dimensions or not? Answers to the question range from the dualism of Descartes, who posited a physical res extensa (ie, dimensional "extended stuff") and a mental res cogitans (ie, the nondimensional "thinking stuff"), to panpsychism, which suggests that consciousness is everywhere to a greater or lesser degree.[62]

Returning to the first question of explanatory frameworks for consciousness (Table 2), there are several theories that are more explicitly physical. One of the most unique and controversial arguments is that consciousness is not generated by classical computational activity in neuronal networks but rather by quantum-physical processes.[63,64] A stated implication of the theory is that general anesthetics suppress consciousness by disrupting quantum coherence across the brain.[6] This is similar in principle to other current theories of general anesthetic mechanism—because it involves a breakdown of coherent information—with a very different physical instantiation. This theory is speculative and, again, controversial. However, there are some initial modeling studies[65,66] and empirical investigations,[67–69] suggesting that anesthetics could potentially function at a subatomic level that involves quantum processes. Whether the fundamental tenets of the theory are ultimately supported or not, fine-grained investigations of how anesthetics interact with the building blocks of physical reality will be uniquely informative.

WHERE DO WE GO FROM HERE?

With humility, I offer some considerations as we move into the next century of investigation.

1. We should embrace the scientific problem of consciousness. The field of anesthesiology is extremely well positioned to play a leadership role in addressing a fundamental scientific question of historic importance. Our collective "laboratory" is composed of operating rooms and critical care units around the

world, in which we guide hundreds of millions of humans through conscious state transitions each year. Major organizations like the American Society of Anesthesiologists and the International Anesthesia Research Society have successfully focused attention on clinical neuroscientific topics, such as perioperative brain health and anesthetic neurotoxicity, respectively. Coordinating efforts around the science of consciousness could result in a major impact and help secure the role of anesthesiology in academic medicine as well as the academy in general.

2. We should study all major dimensions of consciousness. Heretofore, anesthesiology has understandably and appropriately focused on the aspects of consciousness with clinical implications such as intraoperative awareness, delirium, mechanisms of anesthetic-induced unconsciousness, and pain. These are all important topics, but we have the potential to offer much more by engaging in foundational theory, rigorous investigation of the contents of consciousness, the study of pharmacological and nonpharmacological altered states of consciousness, and more. Although we should remain committed to developing anesthetic monitoring modalities and understanding anesthetic mechanism of action, we should not be parochial and miss the opportunity to engage in multiple dimensions of this rich scientific inquiry. Furthermore, related neuroscientific topics like memory and attention should be considered in this context, given their scientific importance and clinical relevance to anesthesiology.
3. We should collaborate broadly and be team leaders. Consciousness is multidimensional and thus requires multidisciplinary team science. Anesthesiologists cannot address every aspect of consciousness, but we can be intellectual leaders and catalysts that help coalesce the appropriate talent and required expertise. Neuroscience, cognitive science, computer science, psychology, engineering, neurology, psychiatry, neurosurgery, physics, and philosophy are key disciplines that we can engage and organize to achieve major impact.
4. We should publish and present both within and outside of anesthesiology. It is important to discuss and to publish on consciousness in anesthesiology conferences, journals, and textbooks. However, anesthesiologists also need to transcend and redefine traditional boundaries to have a presence in forums beyond our field. This is one important approach to establishing the connectivity, credibility, and reputation to be influential in the study of consciousness.
5. We should work across multiple neural scales and across the translational spectrum. Given the realities of our clinical practice, there has been a natural and understandable focus on electroencephalographic research related to consciousness in the field of anesthesiology. This has important clinical applications, but we must take a multimodal approach, with continued engagement and enrichment in functional neuroimaging, nonhuman primate neurophysiology, neural spike activity analysis, causal manipulation of neural circuits, and computational modeling. Furthermore, we must actively synthesize knowledge that has been gained across neural scales to achieve comprehensive understanding and across translational phases to achieve broad clinical relevance.
6. We should educate future generations of anesthesiologists about consciousness. If we desire continued engagement in the science of consciousness, which will take decades to fully develop, then we must educate and inspire future anesthesiologists and physician-scientists. Training related to what is known and unknown about consciousness should be a part of our residency and fellowship curricula, reflecting the fundamental physiology and neuroscience of our field. Anesthesiology residents complete their training knowing how to manage anesthetic state transitions but have little formal training in the underlying neurophysiological mechanisms or the broader context of consciousness science. Furthermore, enhancing the visibility of anesthesiology's commitment to important intellectual and scientific pursuits can inspire and attract more physician-scientists to our field.
7. We should advocate and engage with the broader community. It is not sufficient for us to take on the problem of consciousness. We need to inspire others to collaborate with us, excite them about what we have to offer, educate them about what we need to accomplish our vision, and proactively define our academic narrative and identity. This level of engagement must range from the lay public to major scientific funding agencies.

Finally, we should be bold. Anesthesiology should be the field that commits to solving the problem that many shy away from for fear that it is unsolvable. If there is one research program that can fully occupy us for the next century, it is how the electrical and chemical activities of the brain generate our perception, perspective, pain, and poetry. As biologist and anthropologist Thomas H. Huxley once remarked, "How it is that anything so remarkable as a state of consciousness comes about as the result of irritating nervous tissue, is just as unaccountable as the appearance of the Djinn when Aladdin rubbed his lamp." We are the only field that is truly expert at putting that genie back into the lamp and bringing it out again at will—the rigorous, multidimensional, and multidisciplinary investigation of those experiential transitions represents a tremendous opportunity to help reveal the magic of consciousness in the next 100 years of anesthesiology .

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