PREFACE

Although millions of people worldwide are anesthetized every year, we still have no true understanding of why the drugs we use do what they do. This remarkable lack of knowledge limits our ability to design drugs that would minimize or eliminate anesthetic side effects. Indeed, our anesthetic drugs are powerful poisons. The therapeutic index is defined as the lethal dose that kills 50% of the population divided by the effective dose for 50% of the population. For many drugs, the therapeutic index is several hundred or thousand fold; for anesthetics, the therapeutic index is only 3–4. This narrow margin of safety underscores the inherent danger of anesthetics. It is only because of the skill of well-trained anesthesiologists that anesthesia is relatively safe. Nonetheless, whereas serious complications such as death are rare, more bothersome complications (nausea, vomiting) are common, and are terribly distressing for patients. Only by thoroughly understanding how anesthetics exert their effects (good and bad) can we design drugs that will do one thing and one thing only—anesthetize patients, rendering them unconscious, amnestic, and insensible to noxious stimulation.

Neural Mechanisms of Anesthesia represents our current understanding of anesthetic mechanisms. Its emphasis is rather different from other books on the subject, which in the past focused primarily on molecular mechanisms. We have chosen to examine anesthetic mechanisms at multiple levels: the molecule, the cell, organ systems, and the whole body (Fig. 1). This broad overview is necessary, we believe, because it is difficult to grasp the impact and importance of an experimental finding in the absence of the context of the whole animal or human. For example, when a researcher reports that isoflurane enhances opening time of a particular channel, what does that mean to a clinician? How does that action result in the clinically relevant actions of anesthetics (such as unconsciousness)? Furthermore, how much effect on opening time is required to get the relevant result? If the researcher reports that isoflurane at one minimum alveolar concentration enhances channel opening time 10%, is that sufficient to achieve a clinical goal? One can see the fundamental flaw in not being able to link these specific experimental findings with clinical observations. If we knew through some independent means that 50% enhancement (exclusive of any other action, an important and probably incorrect caveat) was required to cause unconsciousness, then we could conclude that this effect on opening time is not relevant. Thus, we must synthesize all the experimental findings at multiple levels in order to determine the relevance of each. Claude Bernard, the eminent 19th century scientist, clearly recognized the folly of narrowly viewing experimental findings:

> ... If we break up a living organism by isolating its different parts, it is only for the sake of ease in analysis and by no means in order to conceive them separately. Indeed when we wish to ascribe to a physiological quality its value and true significance we must always refer it to this whole and draw our final conclusions only in relation to its effects in the whole—CLAUDE BERNARD, 1865

Each researcher clearly examines the problem of anesthetic mechanisms from a different perspective, not unlike the six blind men of Indostan, who "examined" the elephant, each having different ideas about the elephant's shape. In the end, though, the blind men had incomplete "visions" of the elephant:

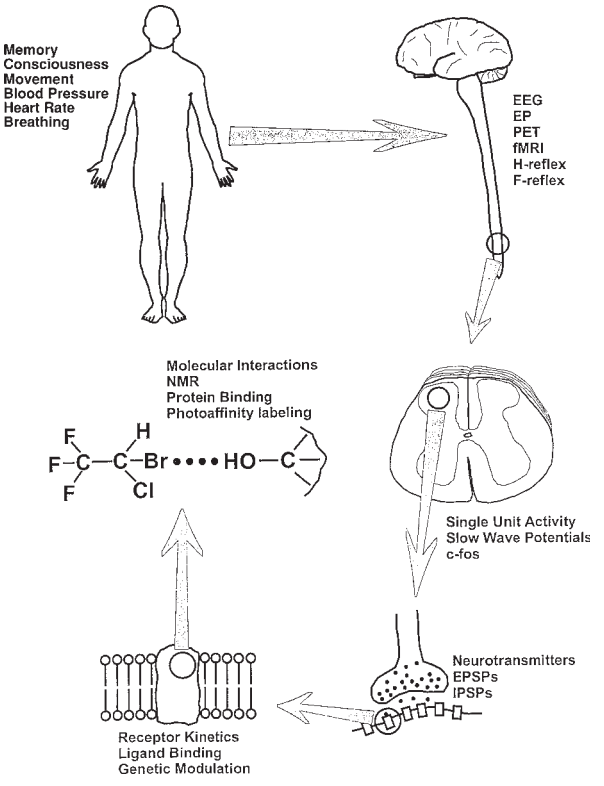

Fig. 1. Anesthesia results in clinically observable effects, such as amnesia, unconsciousness, and immobility. Anesthetic mechanisms must explain these endpoints, and are investigated by study of smaller and smaller components of the organism, such as the brain and spinal cord, the dorsal horn of the spinal cord, the synapse, the cell membrane with its associated receptors and proteins, individual receptors, and finally individual molecules, including molecular interactions between anesthetics and specific sites on proteins and other biological molecules. EEG = electroencephalogram; EP = evoked potentials; PET = positron emission tomography; fMRI = functional magnetic resonance imaging; EPSPs = excitatory postsynaptic potentials; IPSPs = inhibitory postsynaptic potentials; NMR = nuclear magnetic resonance. Other methods to investigate anesthetic mechanisms are available but have been omitted.

And so these men of Indostan
Disputed loud and long,
Each in his own opinion
Exceeding stiff and strong,
Though each was partly in the right,
And all were in the wrong!
—JOHN G. SAXE, *The Blind Men and the Elephant*

So, too, is our understanding of anesthetic mechanisms incomplete. This book will hopefully bridge the gaps that exist between the various views and perspectives of the contributors.

We have separated *Neural Mechanisms of Anesthesia* into six sections. The first section discusses the history of research into mechanisms of anesthesia. The second section covers topics related to consciousness and memory. These chapters are important simply because before we can discuss how anesthetics work, we must decide what they affect. Ablation of nociceptive motor responses, a third critical anesthetic endpoint is included in Chapter 11. The third section includes chapters describing physiological (sleep) and pathophysiological (coma) states related to anesthesia. Section 4 (Neural Mechanisms) reviews the anatomic structures and physiological processes that are likely targets of anesthetics. A well-grounded knowledge of the cerebral cortex, thalamus, reticular formation, and spinal cord will aid the reader's understanding of chapters dealing with anesthetic action at these sites. The fifth section includes cellular and molecular mechanisms. We have included chapters on drugs that are not truly general anesthetics, but are used in clinical practice and can affect the action of general anesthetics (local anesthetics, opiates, neuromuscular blocking drugs). Lastly, we end with a chapter on the future of research into anesthetic mechanisms.

What is anesthesia? This simple question does not have a simple and straightforward answer. Ask any number of individuals and one is likely to get different answers. For the surgeon, general anesthesia consists of an immobile patient. For the patient, general anesthesia consists of amnesia, and not necessarily unconsciousness. That is, patients would likely choose the combination of amnesia and consciousness over the combination of recall and unconsciousness. The latter combination is possible, at least as regards implicit recall. For the anesthesiologist, general anesthesia entails immobility, amnesia, and unconsciousness. Other goals are desirable, but not necessary. Some argue that analgesia is needed, but we disagree. We defend this position first with a semantic argument. Analgesia, in its simplest form, is defined as relief of pain. Pain is the conscious awareness of a noxious stimulus (real or perceived) associated with certain emotional and behavioral patterns, such as withdrawal. Because anesthetized patients are usually unconscious, they do not perceive pain. Of course, they may develop physiological responses to the noxious stimulus (increased heart rate, blood pressure, catecholamine concentrations, etc.). But when awakened and asked if they "felt any pain" they would say: "None—I was completely knocked out." In some patients, amelioration of these physiological responses is desirable (such as those with coronary heart disease). However, in a healthy young patient, a heart rate of 130 bpm and blood pressure of 180/90 mmHg is not injurious. And, whether or not this response is harmful because of a failure to obtain pre-emptive analgesia is open to debate.

Figure 2 summarizes the sensitivities of various anesthetic goals or endpoints. It is important to point out that the sensitivities of memory and consciousness are similar, but that available evidence suggests that memory is more sensitive to anesthetics. These data, however, were developed in human volunteers who were not subjected to noxious stimuli. It is possible that noxious stimulation would shift both the memory and consciousness curves to the right. Because of ethical concerns, these studies have not been performed, and are not likely to be performed. The greater sensitivity of memory parallels the greater sensitivity of memory to other insults, such as trauma and ischemia. For example, minor head trauma can lead to just a few minutes of unconsciousness but hours of amnesia (both retrograde and antegrade). Both memory and unconsciousness are more sensitive than the movement response to noxious stimulation. This is in keeping with the importance of the withdrawal (flight) response. From an evolutionary perspec-

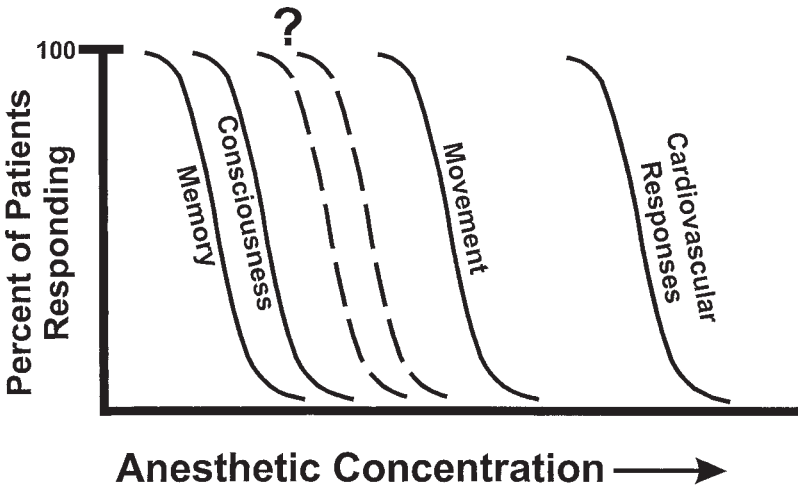

Fig. 2. Anesthetic endpoints have different sensitivities to anesthetics. Memory and consciousness are particularly sensitive, and ablated well below the concentrations needed to prevent movement. The effects on memory and consciousness have been examined primarily in human volunteers in the absence of noxious stimulation. It is quite possible that noxious stimulation shifts the memory and consciousness response curves to the right, although this is not known with certainty (thus, the question mark). Cardiovascular responses to noxious stimulation are very resistant, and require anesthetic concentrations well above those needed to ensure immobility.

tive, the withdrawal response to a noxious stimulus should be hardy and most resistant to physiological insults, as compared to consciousness and memory. Indeed, simple organisms have nociceptive withdrawal responses, but it is unclear whether they experience consciousness in a way similar to humans. These organisms probably do not have memory (as we know it), but they are capable of "learning," which means that classical conditioning can occur.

Neural Mechanisms of Anesthesia represents the most recent advances in research of anesthetic mechanisms. In part, progress in this research has advanced as a result of our increasing understanding of whole-body, cellular, and molecular processes. The mechanisms of anesthesia are still elusive, but we are closing in. Soon we will be able to design drugs that have specific desired actions, with no undesirable effects. We must continue to carefully judge the risks and benefits of the powerful and dangerous drugs that we use. When describing Morton's use of ether in Boston, Bigelow wrote: "Its action is not thoroughly understood, and its use should be restricted to responsible persons." This statement still rings true 150 years later.

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2

Mechanisms of Consciousness with Emphasis on the Cerebral Cortical Component

G. Bryan Young

INTRODUCTION

Concepts of Consciousness

Consciousness has been defined as an awareness of oneself and one's environment *(1)*. This simple definition fails to account for the many discrete yet interrelated components of conscious awareness. We still do not have a complete understanding of how these components are integrated to produce conscious awareness, partly because consciousness is such a subjective, ephemeral subject. Nonetheless, considerable gains have been made in revealing details of the components and their interaction, e.g., alertness, attention, sensory processing and perception, memory mechanisms and executive functions. Neurophysiological techniques and functional neuro-imaging have helped understand the normal brain. Disease states and the differential effects of drugs (including anesthetics) have also provided insights into components of consciousness and how these elements contribute to integrated brain function.

The main components of consciousness are alertness and awareness. Each of these has subcomponents.

Alertness

Alertness refers to simple wakefulness behavior: the eyes are open in wakefulness; the patient can be roused from a sleep-like state to an eyes-open state; spontaneous wake and sleep cycles usually occur. The absence of this capacity–unarousable unconsciousness–is referred to as coma. Although a considerable amount of processing may occur in the comatose brain, alertness is essential for apperception, conscious appreciation and, usually, for later recall of this activity.

Many years ago, Morruzi and Magoun *(2)* demonstrated that the arousal component of consciousness, including (cerebral cortical) EEG activation, was dependent on the ascending reticular activating system (ARAS). The ARAS was first thought to be an undifferentiated collection or network of neurons with interconnections and projections from the rostral brainstem reticular formation through the thalamus to the cerebral cortex. This concept has been refined. There are not only some alternative pathways that produce EEG activation, but this "network" is composed of discrete systems with various neurotransmitters. Selective gating takes place in subcortical structures, allowing for the selection of information. Thus subcortical regions are important not only for primitive arousal and maintenance of the alert state, but also for components of awareness. This idea is discussed in detail in Chapter 8. Alertness and arousal are dependent on subcortical function (Fig. 1); indeed arousal can occur without a functioning cerebral cortex (*see* persistent vegetative state discussed below).

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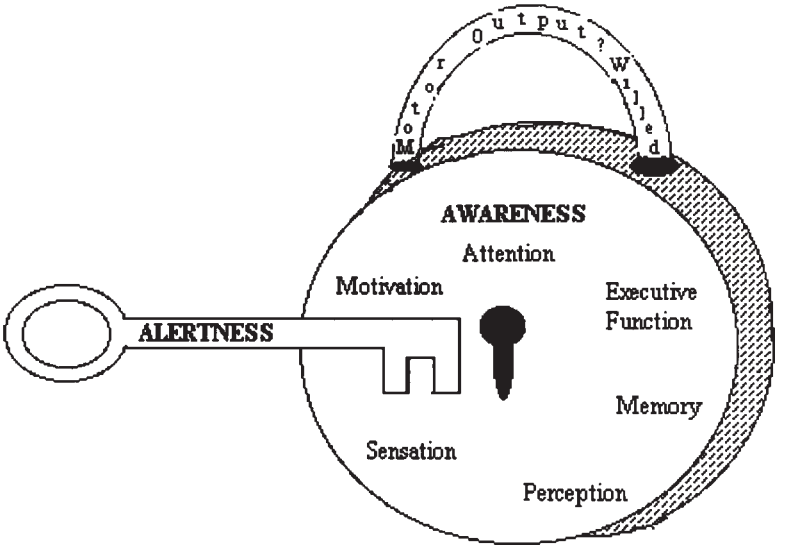

Fig. 1. This cartoon analogy illustrates the essential enabling effect of alertness (a function of the ascending reticular activating system) on awareness. Awareness (the body of the lock) has multiple associated components mainly represented in the cerebral cortex, but with subcortical interactions. The resultant motor output (the mobile shackle) results from processing in the cortical-subcortical system. Whether any action is truly willed or not is still debated.

Awareness

Unlike alertness and arousal, awareness is dependent on the cerebral cortex, but there are essential cortical-subcortical, especially cortical-thalamic, interactions for this more complex and higher form of consciousness. The persistent vegetative state represents alertness without awareness. In this condition the patient can be roused from sleep, shows spontaneous wake and sleep cycles but manifests no evidence of perception, comprehension, memory function or any meaningful reaction or purposeful behavioral response to internal or external stimuli. The persistent vegetative state is most commonly associated with diffuse cerebral cortical dysfunction (as from anoxic-ischemic or hypoglycemic damage). It may also be produced by white matter lesions that disconnect cortical regions from each other and the thalamus (as if diffuse axonal injury from trauma). It may also be produced by thalamic damage that preserves the arousal component, but prevents the transfer of other information to the cortex *(3)*.

There are a number of components of consciousness (*see* Fig. 1) that, in the intact, aware human, do not function in isolation. These are presented separately for purposes of discussion:

Sensation and Perception

Sensation relates to the awareness of a reception of signals from sensory receptors. Sensations have discrete or modular primary sensory receiving areas in the cerebral cortex and association areas for further processing. Primary sensory modalities include somatosensory, visual, auditory, vestibular, olfactory, gustatory, and visceral sensations (*see* Fig. 2). Sensations have temporal (timing relative to the present), spatial (reflecting part of the body plus or minus various regions of extrapersonal space) characteristics and are specific to certain modalities (e.g., visual sensation is separate from somatosensory and auditory senses, even when all refer to the same extrapersonal object). Each primary sensory area of the cerebral cortex has forward and backward connections with association areas; i.e., there is not a one-way mechanism of analysis. Furthermore, both serial and parallel processing of information occur within each sensory system.

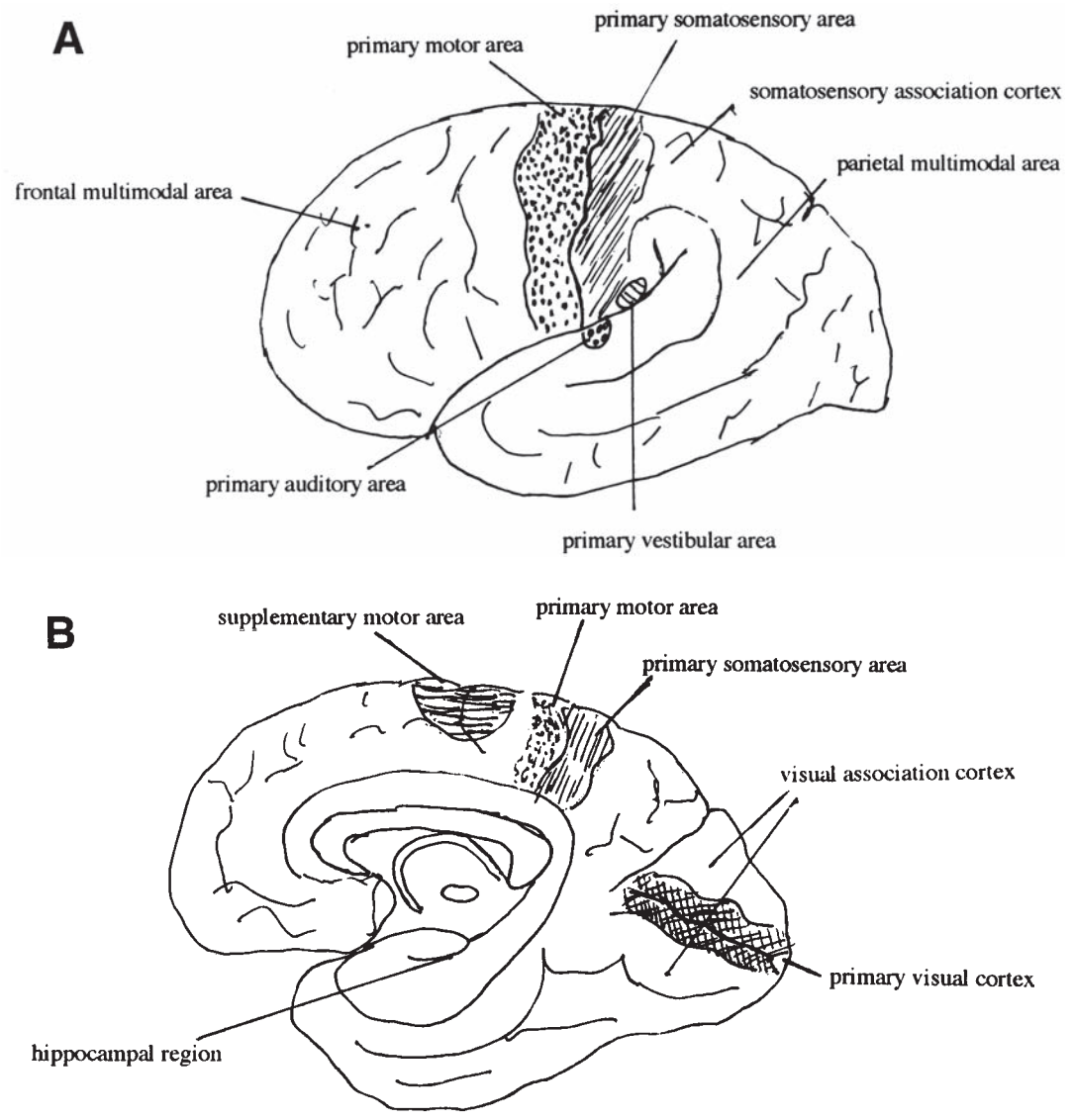

Fig. 2. Various cortical functions are represented in drawings of the convexity **(A)** and mesial **(B)** surfaces of the cerebral cerebral hemisphere.

Perception refers to the further processing of sensory information, providing a symbolic concept of what is happening in the external world. Usually, perception overrides sensation, so that we are aware of an external event or object rather than the fact that we are receiving a sensation. In object vision, the image is segmented into background and foreground and the impressions are fused into shapes and objects. The conscious appreciation of the object involves reception by the primary visual cortex, processing in the visual cortex, transfer to visual association areas and links with visual memory stores. In addition, the focusing of attention is necessary for awareness to occur. If the primary visual cortex is destroyed or isolated (even though it may be activated), conscious awareness does not occur. This is not to deny the occurrence of blindsight (a meaningful response to the visual stimulus, even though the patient denies the awareness of the stimulus). This illustrates the necessary interaction of a number of cortical areas for awareness.

Attention

Moscovitch *(4)* defined attention as

> "a control process that enables the individual to select, form a number of alternatives, the task he will perform or the stimulus he will process, and the cognitive strategy he will adopt to carry out these operations."

Attention includes directivity and selectivity of mental processes. There is a close physiological relationship among attention, alertness and perception.

The anatomical location of cortical regions involved in attention include the anterior cingulate cortex and the inferior parietal lobule, with strong links to subcortical regions, including the thalamus, the reticular formation, and the superior colliculus. Motor inattention occurs with lesions of the dorsolateral frontal region. Akinetic mutism, a condition in which the patient appears awake and visually tracks moving objects, but does not otherwise respond to stimuli, may result from lesions of the mesial frontal cortex or the centromedian-parafascicular thalamic nuclei.

Memory

The neurophysiological basis of memory is unsettled, but enhancement of synaptic connections (either by facilitated neurotransmitter release by long term potentiation or by the physical increase in numbers and locations of synapses) underlies various forms of memory and learning *(5)*. *Working memory* refers to the short term retention of mental activities held in consciousness for immediate use; lesions of the dorsolateral prefrontal cortex have been found to alter visual working memory in monkeys *(6)*. *Anterograde memory*, the laying down of new explicit or declarative memories, and the appropriate retrieval of stored memories, appear to depend on the integrity of function of the mesial temporal structures, probably the hippocampus and/or the entorhinal and perirhinal cortex. Other structures form part of the circuit for anterograde memory: the parahippocampal gyri, the fornices, the medial dorsal or possibly the anterior thalamic nuclei, the cingulum or cingulate cortex and links of these structures. *Remote* or *retrograde memories* are stored outside the mesial temporal regions, as these are preserved in patients with newly acquired bitemporal lesions. *Implicit* and *procedural memories* do not require limbic circuits, at least for the acquisition of motor skills. Patients with bitemporal lesions can learn to play tennis or can retain other information without being able to verbally declare this knowledge without cues. Indeed, Moscovitch *(7)* has proposed that only explicit, not implicit, memories are accompanied by conscious awareness.

Motivation and Emotion

Motivation refers to a drive that helps to determine behavior. It depends on perception, attention, memory, and emotions that function in an interrelated fashion. Important structures in the generation of internal feelings and motivation are the amygdala, the hypothalamus, and associated limbic structures. The hippocampus consolidates information received from regions where sensory and perceptual processing has occurred. The amygdala, by its connections with various cortical and limbic structures, gives the information an affective tone. The posterior insula is also important in the interpretation of the significance of painful stimuli *(8)*.

Language and Other Extended Aspects of Consciousness

Language function, like mathematical ability, is a highly developed cognitive activity of great human importance. The temporal-parietal region of the dominant cerebral hemisphere converts processed information into symbols, allowing an "internal conversation" and conceptual formulation. However, individuals with destruction of this region can still interact with others and show awareness as demonstrated (e.g., by expression in art or other means of nonverbal communication). Thus, language function is not essential for consciousness, although it provides an important dimension to conscious activity.

Extended consciousness is a term that applies to meaningful cognitive function that gives the person a sense of self and a perspective of place and time *(9)*. It is built upon alertness and the various elements of awareness that have been discussed above. Such a process—integrating the previously discussed elements of awareness—involves coordinated function of various cerebral cortical regions in concert with subcortical structures, especially the thalamus. Some areas that are involved in attention, such as the anterior cingulate cortex, may play an essential or initiatory role.

Covert Processing in the Brain

It should be acknowledged that not all processing of information or resultant behavior is consciously directed. Indeed, there is a "phenomenal consciousness," in which the brain registers internal or external phenomena without this mode of processing, demanding attention, or entering into cognitive awareness and decision-making. There is, therefore, a covert or implicit awareness in the brain that is not apparent to the individual at the time. At least, the individual would not admit to it being in his/her awareness! Such phenomena may come into consciousness when they achieve a threshold of meaningful significance that demands our attention. For example, while driving a car, one is not consciously aware of all the stimuli in their fields of vision. However, the individual makes adjustments in speed and steering "without thinking". When, however, something appears that has special significance, e.g., a flashing red light, it receives conscious attention. A chain of events is initiated because of the symbolic importance of the flashing red light. Thus, much processing involving visual, memory areas, the amygdala, somatosensory, motor and other regions goes on without our conscious awareness, but full conscious awareness is called upon when our attention is demanded for important decisions.

Anatomical, Physiological, and Neurochemical Aspects

The cerebral cortex is anatomically and physiologically arranged in a modular fashion of radial columns at right angles to the surface, approx 3 mm in diameter (*see* Fig. 3). Within these vertical columns, pyramidal cells are the most prominent neurons, with basal dendrites extending horizontally, apical dendrites extending vertically, and axons projecting downwards. The latter have recurrent collaterals that excite other pyramidal cells in the same column, producing excitatory post synaptic potentials or EPSPs. The main intrinsic excitatory neurotransmitter is glutamate. Inhibition is an intracortical phenomenon produced by inhibitory interneurons that release gamma-amino-butyric acid (GABA). GABA acts on receptors linked to chloride channels, causing neurons to become hyperpolarized and producing inhibitory post-synaptic potentials (IPSPs). GABA receptors are on or near the neuronal cell body and the axon hillock where action potentials are generated. Since post-synaptic potentials decline spatially and because the net polarity of the neuronal membrane at the axon hillock (the site where action potentials are generated) relates to the net summation and subtraction of post-synaptic potentials, the inhibitory process is strategically placed and potent.

Cortical columns are interconnected by horizontal, laminar connections of neuronal processes. In addition, various cortical regions are interconnected by subcortical fibers of various lengths. The strength of cortical interconnections is greatest for nearby areas, and falls off with distance. Thus interconnection density is inversely related to distance. The axons interconnecting adjacent cortex are mostly of small diameter, allowing a conduction velocity on average of only 5.5 m/s. This results in a limiting of synchronous activity (resonance) of 50–100 ms or 10–20/s. However, some axons have larger diameters and greater conduction velocity. Many are dedicated for longer interconnections, e.g., to homologous regions in the opposite cerebral hemisphere via the corpus callosum. This allows for some rhythms of greater frequency.

The main afferents to the cerebral cortex come from the thalamus. There is an elaborate gating mechanism for this projection (*see* Chapter 8). The main output from the cortex is from pyramidal

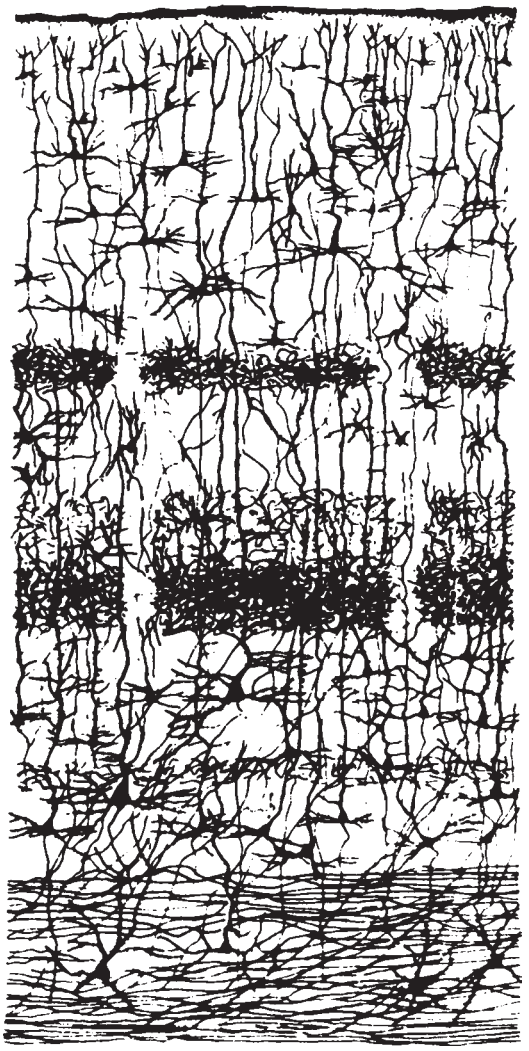

Fig. 3. This is a composite drawing of neurons with their dendrites and superimposed axonal plexuses, illustrating both the vertical columnar arrangement as well as the laminar interconnections of neurons. (Modified from F. O. Schmidt and F. G. Worden [eds.] (1979) *The Neurosciences 4th Study Program* MIT Press, Cambridge, with permission).

cells that project to the basal ganglia and to a lesser extent, the thalamus, brainstem and spinal cord structures.

Steriade and colleagues *(10)* have shown that most cortical rhythms, except for sleep spindles, are generated intrinsically in the cortex. The thalamus plays a modulating or facilitatory role in these rhythms. It has been proposed that a 40 Hz or gamma rhythm is important in allowing for consciousness and integrated brain function. This is produced by circuits during attention and sensory processing tasks that require attention and the "binding" of processed sensory information with memory, attention, and motor responses *(11)*. This rhythm is synchronous across various regions linking thalamocortical networks as well as the hippocampus and neocortex. It has been proposed that such coherent rhythms provide a timing reference that fosters simultaneous or parallel brain activity in a networked rather than purely hierarchical fashion. In this way, for example, all modalities of an

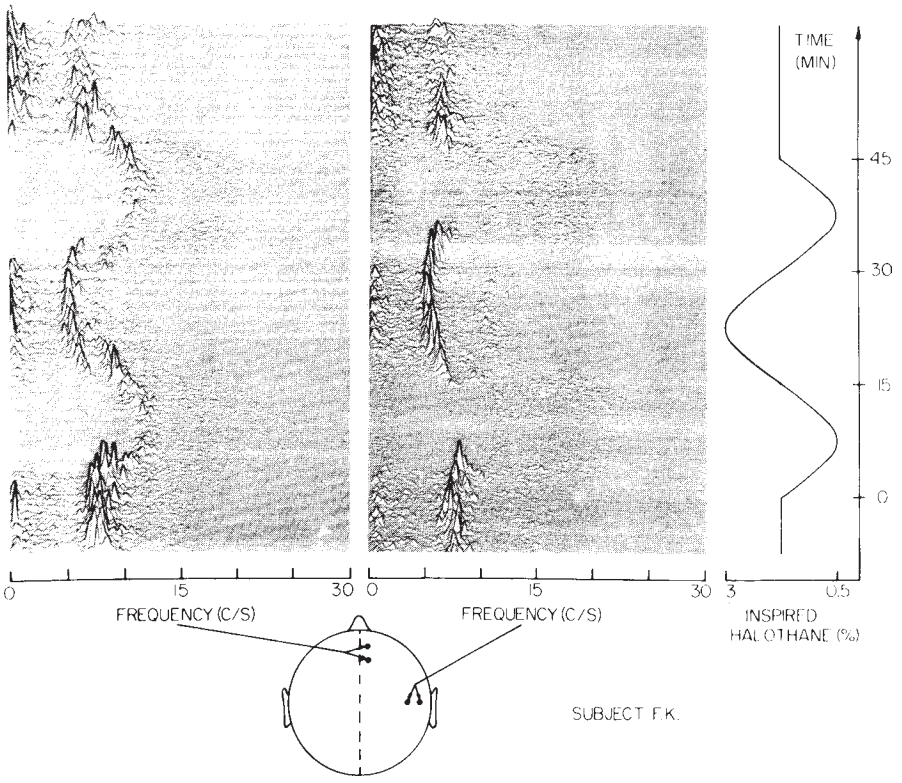

Fig. 4. The power spectrum of the human EEG with different inspired concentrations of halothane. Note the shift to lower frequencies, especially in the frontal region, when the halothane concentration is increased. (reproduced from Nunez, P. Electrical Fields of the Brain. The Neurophysics of EEG. Oxford:Oxford University Press, 1981, with permission.)

object held in memory can be appreciated. It has been found, however, that low voltage fast EEG activity patterns, similar to the gamma rhythm, occur in sleep and in the anesthetized state *(12)*. It may be, however, that there are different types of gamma rhythms (e.g., with varied degrees of synchrony, each with a different physiological significance) or that such unified activity is essential for awareness even though it may occur at other times.

CEREBRAL CORTICAL EFFECTS ON CONSCIOUSNESS PRODUCED BY ANESTHETICS

Most anesthetics decrease net neuronal activity; EPSPs are reduced or blocked in the anesthetic state. Small changes in synaptic gain can have marked effects over large neural systems prior to major blocking effects on individual neurons. Thus, the effects of anesthetics are noted in global or integrated brain function, before individual neurons are silenced.

Many anesthetics have a significant effect on the cerebral cortex, in addition to their profound subcortical effects *(13,14)*. Indeed, Kellaway et al. *(15)* showed that the effects of anesthetics on the isolated cerebral cortex were similar to those on the intact brain. Cortical rhythms of higher frequency affect a wider region of cortex in the normal brain; this high frequency "resonance" is inhibited by anesthetics, causing a coordinated shift to lower frequency spectra (Fig. 4) *(16)*. One high frequency resonance to be affected is the previously mentioned 40-Hz gamma rhythm. With increasing anesthetic dose, rhythmicity is lost altogether.

TOWARDS AN INTEGRATED MODEL OF CONSCIOUSNESS

Consciousness is likely the result of integrated function of multimodal states of the brain. While anyone who attempts to explain consciousness is doomed to be considered reductionalistic, certain aspects can be explained. These isolated components provide at least a glimpse into brain organization and allow for hypotheses about how consciousness arises out of the various processes. There are certain prerequisites to conscious awareness; these include alertness and the ability to attend to certain functions. It is essential that there are interconnections of the various processes or components of awareness. When inter-regional coactivations have not been shown by functional neuro-imaging, it might be that these tools are too crude to note the various subtle but essential interconnections. The mystery is that consciousness is more than the sum of its parts. Strategies are needed that go beyond existing approaches.

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