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Editorial Views

The Mechanism of General Anesthesia

THE PRACTICE OF ANESTHESIA has come a long way. We no longer rely on a half bottle of rum or brandy to induce a state of relative insensibility as a preliminary to major surgery. These and other more-or-less concentrated solutions of ethanol have been relegated to their more appropriate role as tranquilizers—and even in this, they are being superseded by the more fashionable cannabis.

The modern anesthesiologist has at his disposal a variety of remarkably effective agents, with which he can obtain and maintain almost any degree, type and duration of anesthesia desired, with minimal risk to his patient. One can reasonably claim that the great advances in anesthesiology (including patient care) that have marked the last decades have done more than any other factor to make possible the spectacular achievements of contemporary surgery.

The astonishing feature of this rapid evolution in the practice of anesthesia is that it has not been accompanied by a comparable development in our understanding of how anesthetic agents work. This fact is well brought out by the article from the Vishnevsky Surgery Institute of Moscow, in this issue.[1] As these authors point out, it is still taken very much for granted that a depression of the brain-stem reticular formation is the fundamental mechanism of general anesthesia. Like all useful theories, this has helped greatly in providing a relatively simple framework for integrating manifold observations and ideas. Its main assumptions are that "reticular" activity has a tonic excitatory action on the part of the brain where conscious processes are developed—this is usually believed to be the cerebral cortex, but some other forebrain and/or brain-stem areas may well be essential—and when this tonic action is removed, consciousness also disappears. A second postulate follows from the heterogeneous character of the "reticular formation"; it is believed to be made up of large numbers of cells, forming a complex multisynaptic network, into which is funnelled all sensory information relayed to the brain by the various afferent pathways. The essential point is the multiplicity of synapses: if one believes that synaptic transmission is always the weakest point in the transfer of information along neuronal lines of communication, one can expect that a line containing several such weak points in series must inevitably have a low safety factor. Hence the notion that general anesthetics, having the same kind of depressant effect on all cells, will "block" the reticular formation first and foremost, and that the clinically observed loss of consciousness is mainly a secondary effect, resulting from the disappearance of the reticular ascending tonus.

Although these assumptions have not been proved to be altogether incorrect, they oversimplify the real situation. For example, it is now known that reticular stimulation can cause inhibition of at least some cortical neurons[2] and that there is no simple relation between consciousness and the amount of cortical activity: fast EEG activity can be associated with either wakefulness or very deep sleep[3]; corti-

cal arousal is often associated with temporary increases in neuronal excitability,[4] but the mean frequency of firing is not necessarily higher in the awake state—though the *pattern* of firing may be significantly different.[5] Some of the criteria previously used to assess cortical excitability, such as the amplitude of evoked responses, are too ambiguous for a precise analysis since synaptic potentials make up the main component of gross evoked responses, and therefore very large waves may be evoked in the total absence of cellular firing.[6]

Similarly, there is reason to believe that all anesthetics may not act alike, and that they do not necessarily affect all cells equally. For one thing, different synapses have widely different safety factors: in general, the first central synapses in the direct afferent pathway, such as those in the dorsal column nuclei or the lateral geniculate body, can conduct impulses at very high frequencies, and they are very resistant to anesthetics and other depressant agents. By contrast, the monosynaptic dorsal root–ventral root connection cannot be driven at a high frequency, and it is readily blocked by anesthesia. But other synapses, as in the nigral–caudate excitatory pathway, though capable of high-frequency transmission, are extremely vulnerable to some general anesthetics (especially barbiturates). In yet another variant, we have synapses which transmit only at low frequencies but are very insensitive to anesthesia; a good example of this is the thalamic relay in the primary somatosensory pathway. However, the frequency-limiting factor at this site is the operation of a powerful and prolonged recurrent inhibitory action ("negative feedback"), rather than a low safety factor of excitation as in the spinal monosynaptic connection.

Many neurophysiologic studies in the last decade have shown the prominent role played by inhibitory control in cerebral function, as well as in the spinal cord.[7] This has led to suggestions that some anesthetics may either facilitate inhibition [8] or alter the balance between excitatory and inhibitory influences [9] so as to reduce overall activity.

In general, anesthetics tend to depress spontaneous and repetitive activity long before there is any marked effect on the transmission of primary short-latency responses. This is to be expected, since the latter type of activity is usually mediated by a much more powerful synaptic action. There is evidence that in the cerebral cortex conscious processes are dependent on a high degree of spontaneous and repetitive activity,[10] and that this is promoted by the action of acetylcholine—probably liberated by the activity of an ascending cholinergic system, which can be equated with the reticular arousal system.[11, 12] Some recent observations strongly suggest that acetylcholine acts in a rather special way in this case, by reducing the neuronal permeability to potassium ions.[13] This has two effects: it tends to cause depolarization and thus excitation, and it also enhances the tendency to prolonged repetitive discharges. This mechanism seems peculiarly appropriate as a means of establishing conscious processes, and it is therefore significant that some general anesthetics have been shown (though so far only in lower animals [14, 15]) to have the very opposite effect of increasing the permeability to potassium ions. There is some reason to think that these anesthetics may act primarily by depressing cellular metabolism and that this leads to the specific change in membrane permeability.[16]

The Russian authors are thus rightly emphasizing the need for a closer and less unquestioning look at the mechanisms of action of anesthetics at different sites in the brain. Some careful recent studies,[17, 18] at the level of single cells in the spinal cord, which indicate differential pre- or postsynaptic actions of barbiturates and volatile anesthetics, are steps in the right direction. But we need to know much more about this subject: not just to have knowledge for its own sake, but because even more effective and safer procedures and drugs cannot be expected to come our way solely through a process of random trial and error.

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Minipigs, Microsomes, Metabolism, and Maupassant

"O, ma pauvre, Mathilde! Le mienne était fausse."
The Necklace, Guy de Maupassant

The article by Sawyer *et al.* in this month's issue of ANESTHESIOLOGY must generate much food for thought. Only six years ago pharmacology students were taught categorically that, almost unique among drugs, inhalation anesthetics entered and left the lungs essentially unaltered by cohabitation with the body's biochemical machinery. At that time the golden era of study of uptake and distribution of these agents was in progress. Numerous computer-programmed multicompartmental analyses concerned with the uptake of anesthetics appeared, based primarily on the variables of blood flow and partition coefficients. There was no "sink" programmed for metabolism—it just did not exist.

Then, in swift succession, several investigators determined this view of metabolic inertness of anesthetics was untenable. Van Dyke, Chenoweth and Van Poznak[1] found that ether, methoxyflurane (Penthrane), and halothane (Fluothane) were metabolized to a considerable extent in animals, a finding documented and investigated further by Cohen[2] and others. The magnitude of halothane metabolism in man was determined by Rehder *et al.*[3] This group of German investigators found that as much as 20 per cent of absorbed halothane was metabolized, a surprise indeed. Like the denouement of a de Maupassant short story, Holaday and coworkers[4] topped this by discovering that 50 per cent of absorbed me-