aldosterone system during cardiac surgery with morphine–nitrous oxide anesthesia. ANESTHESIOLOGY 42:538–544, 1975
5. Miller ED Jr, Bailey D, Kaplan J, et al: The effect of ketamine on the renin–angiotensin system. ANESTHESIOLOGY 42:503–505, 1975
6. Miller ED Jr, Longnecker DE, Peach MJ: The regulatory function of the renin–angiotensin system during general anesthesia. ANESTHESIOLOGY 48:399–403, 1978
7. Wang H, Epstein RA, Markee SJ, et al: The effects of halothane on peripheral and central vasomotor control mechanism of the dog. ANESTHESIOLOGY 29:877–886, 1968
8. Price ML, Price HL: Effects of general anesthetics on contractile response or rabbit aortic strips. ANESTHESIOLOGY 23:16–20, 1962
9. Sprague DH, Yang JC, Ngai SH: Effects of isoflurane and halothane on contractility and the cyclic 3′–5′-adenosine monophosphate system in rat aorta. ANESTHESIOLOGY 40: 162–167, 1974
10. Perry LB, Van Dyke RA, Theye RA: Sympathoadrenal and hemodynamic effects of isoflurane, halothane and cyclopropane in dogs. ANESTHESIOLOGY 40:465–470, 1974
11. Miller ED Jr, Gianfagna W, Ackerly JA, et al: Converting-enzyme activity and pressor responses to angiotensin I and II in the rat awake and during anesthesia. ANESTHESIOLOGY 50:88–92, 1979

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50:84–87, 1979

Anesthesia and Learning

IN THIS ISSUE, Adam and Collins report the effects of enflurane on reaction time of human volunteers.[1] Their experiment attempted to evaluate effects of enflurane on short-term memory and motor function. The processes of memory and anesthesia appear to be competitive, since memory is an important ingredient of consciousness and anesthesia implies loss of consciousness. They do, however, have much in common. Both are complex processes involving the entire brain and are associated with changes in molecular structures, membrane function, neurotransmission and electrophysiology. Conceptually, studies of the two processes are identical, and must proceed at many levels of brain function. In this editorial we describe how higher mental processes can be studied and how the brain is thought to be functionally organized, and summarize what is known about the neurobiology of memory.

How Function of the Brain is Studied

As Rozin has recently emphasized,[2] the flow of information about complex mental processes, where few hard data are available, must be from psychology to biology rather than in the reverse direction. Although physiologic changes must eventually explain the processes of anesthesia and memory, where and when—given our limited knowledge—do we look for these changes, and how can they be interpreted? Observed changes in molecules, membranes and individual neurons have not been helpful. We must first determine the gross structure of the process psychologically, *i.e.*, by behavioral observation, as was first done for memory by Ribot,[3] who referred to "the conservation of certain conditions, their reproduction; . . ." and James,[4] who described a primary (immediate) and a secondary (long-term) memory. Early analyses of this type were done for anesthesia by Snow[5] and Guedel.[6] The gross structure of the process must then be separated into its component parts (component analysis). Memory processes have thus been divided into sensory reception, coding of sensory data, storage of those data for a short time in a limited-capacity memory bank (primary memory), transfer of those coded data to large-capacity long-term banks (secondary memory), and finally, retrieval of the stored information. The anesthetic process can be divided into sedation, amnesia, analgesia, disorientation, loss of consciousness, and various degrees of reflex depression.

Once the general structure and component parts of a process are outlined, we can then cautiously enter the nervous system in search of the physiologic and biologic bases. But we still need direction lest we wander endlessly and aimlessly through tracts and synapses. We must have some idea of the functional organization of the brain, *i.e.*, which area or interacting areas subserve various mental functions.

How the Brain is Organized

According to Luria,[7] the brain may be divided into three functional units. Each unit has a hierarchical arrangement of three anatomic divisions of increasing levels of function and operates in concert with the other two units. Together they involve the entire brain. The first functional unit regulates "tone" or waking. It consists morphologically of the reticular formation and the medial and mediobasal zones of the cortex derived from the paleocortex, archicortex and intermediate cortex. The function of this unit is to maintain the necessary level of cortical "tone" and thus regulate the alertness necessary for higher cortical function. Lesions in this unit produce a lowering of cortical tone, rapid fatigability, disturbance of consciousness, and deficits of memory.

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The second functional unit of the brain receives, analyzes and stores afferent information. It is located on the lateral, convex surface of the cerebral hemispheres. The primary zones of the unit are the modality-specific projection areas in layer IV of the cortex, which receive input from visual, auditory, vestibular and other sensory receptors. The secondary zones of association neurons in cortical layers II and III code discrete incoming excitation (raw sensory data) into patterned neural activity. The tertiary part of the unit consists of cells in association cortical layers II and III of the overlapping zones of specific modality located primarily in the inferior parietal region. Information reaching this tertiary zone from modality-specific areas is integrated and translated into stable storage forms. It is an area in which modality-specific information is changed into symbolic form.

The third functional unit of the brain is responsible for the organization of conscious activity. The tertiary part of this unit is in the prefrontal cortex. It formulates voluntary programs and regulates complex behavior. It is subserved in these functions by two-way connections with lower levels of the brain and also with most other areas of the cortex. It is powerfully influenced by, and exerts control over, functional unit I. It receives and synthesizes afferent impulses from the rest of the brain and organizes efferent impulses. The secondary zone is located in the pre-motor area and serves to organize motor activity. The primary zone is the motor cortex, whose output is from large pyramidal cells in layer V.

How the Organization of the Brain is Determined

The basis of Lauria's organizational concept, as well as competent analysis of the memory process, derives from observations of the effects of physical and chemical lesions. Brain cells that serve a given function tend to look alike. They also tend to be grouped in the same area, travel along the same tracts, and show selective sensitivity to drugs.[2] Discrete lesions produced by trauma or tumors provide information about the contributions of certain tracts or cortical areas to function. Diseases or toxins that preferentially disturb certain cell types give information about the functions of those cells. Blunt trauma to the head may obliterate all cognitive functions, which usually return in stages. The observed effects of lesions superimposed on a conceptual cerebral organization thus gives us a "ballpark" idea of where to look for the physiologic bases of behavior. Anesthetics can be valuable tools in this detective work because they produce reversible biochemical lesions with dose-dependent effects.

Cellular Correlates of Memory

Information about the physiology and molecular biology of learning began to accumulate in 1943 with the description by Mayer-Gross[8] of retrograde amnesia (destruction of short-term memory) produced by electroconvulsive therapy (ECT). Halstead[9] then suggested that durability of memory might depend on the stability of changes in neuronal nucleoproteins. This suggestion was followed with extensive work by Hydén[10] on the effects of learning on the ratio of RNA to DNA in neurons and glia. Another major step occurred when Flexner *et al.*[11] reported in 1963 that the antibiotic puromycin, a potent inhibitor of protein synthesis, caused loss of memory. Barondes and Cohen[12] demonstrated that inhibition of protein synthesis spares short-term memory but evidently prevents its consolidation into long-term memory. Andry and Luttges[13] have further demonstrated that ECT prevents consolidation of memory by interference with a short-term process. They have also shown that cycloheximide, another antibiotic that impairs protein synthesis, spares short-term memory, but blocks long-term memory.

Although there is considerable evidence that the establishment of long-term memory traces depends on protein synthesis, the injection of protein inhibitors into the brain produces many other effects that could interfere with memory. Furthermore, it has been shown that cycloheximide also inhibits tyrosine hydroxylase and may act by decreasing the functional pool of brain catecholamines.[14] Quartermain and Botwinick[15] have also shown that the amnesia produced by cycloheximide can be reversed by injection of D-amphetamine or monamine oxidase inhibitors, and that alpha-methyl-para-tyrosine (a tyrosine hydroxylase inhibitor) and diethyl-dithiocarbamate (a dopamine beta-hydroxylase inhibitor) produce amnesia similar to that produced by cycloheximide.

Rutledge[16] has shown that stimulation of neuronal networks changes synaptic morphology, and suggests that the presentation of information results in an increase in presynaptic action potentials, increased transmitter release, prolonged excitatory postsynaptic potentials, formation of new postsynaptic membranes with increased dendritic length, appearance of new synaptic elements, including specialized receptors, and growth of presynaptic terminals toward receptors.

A reasonable concept of learning, then, includes sensory stimulation and the development of membrane potential changes in projection and association areas; this constitutes the labile short-term memory trace. With repetitive stimulation and increased transmitter release there is postsynaptic facilitation. This in turn may stimulate the production of messenger RNA and the synthesis of new proteins to effect morphologic synaptic changes that may eventually be identified as the relatively stable trace of long-term memory. It is obvious from this short review that the effects

of anesthesia on lipid membrane systems[17] and subsequent effects on protein conformational changes, ion flux, neurotransmitter release and neuroelectric activity could profoundly alter the storage and retrieval of information in memory.

Evoked-response Correlates of Memory

One more bit of background is pertinent to this discussion. Since neuronal activity produces electrical potentials, it is customary to relate active mental processes to those potentials and to describe the effects of anesthetics on the brain in terms of alterations in those potentials. Single-unit responses recorded from intracellular electrodes give information about transmitter release or responsiveness of postsynaptic membranes. Such data, however, provide little insight into the mechanisms by which anesthesia or learning alters the functions of the brain. Electrical activity is also recorded from larger areas within the brain or from the scalp. Those activities are algebraic sums of potentials occurring at a distance from the recording electrodes.

When action potentials are induced in peripheral afferent pathways, they "evoke" a series of electrical responses when they reach the brain. Thus, electrical stimulation of the ulnar nerve produces a somatosensory evoked response; stimulation of the retina by light, or of the organ of Corti by sound, produces a visual or auditory evoked response. Mental processes are also associated with certain potentials recorded from the human scalp. These are called event-related potentials (ERPs). When such potentials buried in background electroencephalographic activity occur about 300 msec after a certain event, and a computer is programmed to add all potentials from 250 to 350 msec after that event, the random EEG activity (not related to the event) will cancel out and leave the event-related potential exposed. Attempts can then be made to correlate changes in the amplitude and latency of that potential to changes in behavior produced by a drug or lesion. Extreme caution, however, is indicated. We must emphasize that these are event-related potentials. They are merely related in time to a certain psychological event. At present there is only circumstantial evidence that they are electrical manifestations of reported mental processes. There is not yet a means of showing that electrical activity thus recorded is causally related to the event with which it is correlated in time.

Current Work on Anesthesia and Learning

Above we described a scheme for conceptualizing cerebral processes. The first step was a general description of their structures. This was followed by analysis of their components, by deduction of the brain systems involved, and finally by determination of the possible underlying biophysical changes. Considerable work has now been done on the molecular and membrane effects of anesthetics. Only very recently, however, has any interest been shown in the psychological structuring of the anesthetic process. Without knowledge of this structuring, anesthesia cannot be fully understood.

The Sternberg[18] paradigm (task) that Adam and Collins used in their study is straightforward. A list of digits or words (the *positive set*), usually one to six items in length, is shown to the subject, one item at a time. The list is within the memory span (easily remembered by the subject). After the last item has been presented, the subject hears a warning tone and then sees a *test* item. He has been instructed to signal *yes* if the test item occurred in the positive set (the list just presented) and *no* if it did not. His reaction time is defined as the interval between the presentation of the test item and the beginning of his response.

In this task, reaction time typically increases as a linear function of set-size: the time taken to signal yes or no is directly proportional to the length of the list, regardless of whether the test item occurred or did not occur in the list. The reaction time for a positive test item does not depend on where in the set the item appeared: late items and early ones are recognized equally rapidly. Increasing the size of the positive set by one item increases reaction time by a constant amount (approximately 40 msec). These three facts indicate that the set's representation in memory is scanned both serially (one item at a time) and exhaustively before a decision is made. (If the set were not scanned exhaustively, then positive responses would occur sooner than negative ones, since only about half as many items would on average have to be scanned before a positive match was found.) Items early in a list would be recognized sooner than late ones.

The slope of the line that describes reaction time (RT) as a function of set-size is accordingly on the order of 40 msec. If L denotes set-size (that is, the number of items in a just-memorized list), then RT = 40 L + K. The constant K (the zero intercept) is usually on the order of 400 msec. It comprises the time taken to complete all those mental processes that take place between the onset of the test item and the initiation of the subject's response, except the memory search. The slope (40 msec) is presumably the time taken to compare the test item's representation in memory with that of each member of the positive set. Both slope and intercept are sensitive to various types of chronic lesions and drugs, and they can vary independently of one another, so that the one may lie well within normal limits while the other may not.[19]

The following is a suggestion of what may occur during a reaction time test using Sternberg's paradigm.

A subject who has adequate cortical tone generated by functional unit I sees a set of items presented serially. Sensory impulses arrive initially at zone I of unit II and are then encoded into symbolic patterns in zones II and III. The associated neural activity forms a "trace" that exists for a short time. The test item is similarly coded, and its trace is compared sequentially with the trace of every member of the positive set. At the end of this search, a *yes* or *no* (match/no match) decision is made, perhaps in unit III, which then generates the appropriate response program and initiates impulses from the motor cortex. Since the positive set is already in memory, the total reaction time must include the time taken to encode the test digit, search memory, make a decision, and formulate and initiate the motor response. (The figures cited for search time per item and residual reaction time—40 msec and 400 msec, respectively—are average times for normal volunteers.) There is, of course, individual variation.

Each subject tested by Adam and Collins scanned only one set-size of digits. It is therefore impossible to determine either the slope or the intercept of the reaction time function, since at least two points are required to fit a straight line. Consequently we do not know whether the anesthetic affected the slope (the time taken to scan each item in memory) or the intercept (the time taken to perceive, decide, and respond) or both. Their observed correlations between increased latency of late activity in the event-related potential and increased reaction time are interesting and may be of value in the future. To interpret these changes as evidence of slowing of the decision-making process, however, would at this time be sheer conjecture. Adam and Collins further claim to have shown in a previous study[20] that "the averaged scalp potential . . . reflects accurately the search process." Perusal of the reference fails to uncover justification for that statement. While certain late components of the visual evoked response increased in latency as set-size increased, they did not increase at the same rate as reaction time. Furthermore, no attempt was made to determine whether the increase in latency with set-size was independent of the position of the test digit in the set.

Adam and Collins are to be commended for achieving the controlled conditions under which drug effects were measured. Stable conditions at known anesthetic concentrations are difficult and time-consuming to obtain but are essential in any sort of study in which psychological processes are of primary interest. Studies of this sort should be encouraged, because we have only begun the important work of structuring the anesthetic process. Such work, carefully done, will serve to direct the membranologist and synaptologist to where the gold is buried.

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References

1. Adam N, Collins GI: Alteration by enflurane of electrophysiologic correlates of search in short-term memory. ANESTHESIOLOGY 50:93–97, 1979
2. Rozin P: The psychological approach to human memory, Neural Mechanisms of Learning and Memory. Edited by Rosenzweig MR, Bennett EL. Cambridge, Mass., MIT Press, 1976, pp 3–48
3. Ribot TA: The Diseases of Memory. An Essay in Positive Psychology. The International Scientific Series. London, Kegan Paul, Trench and Company, 1882
4. James W: The Principles of Psychology. Volume 1. New York, Henry Holt and Company, 1890, pp 643–689
5. Snow J: Narcotism by the Inhalation of Vapors. From the London Medical Gazette. London, Wilson and Ogilvy, 1848
6. Guedel AE: Inhalation Anesthesia. A Fundamental Guide. New York, Macmillan, 1937
7. Luria AR: The Working Brain. New York, Basic Books, 1973
8. Mayer-Gross W: Retrograde amnesia. Some experiments. Lancet 2:603–605, 1943
9. Halstead WC: Brain and intelligence, Cerebral Mechanisms in Behavior. Edited by Jeffress LA. New York, John Wiley and Sons, 1951, pp 244–272
10. Hyden H: RNA—a functional characteristic of the neuron and its glia, Brain Function II, RNA and Brain Function Memory and Learning. Edited by Brazier MAB. Berkeley, University of California Press, 1962, pp 29–68
11. Flexner JB, Flexner LB, Stellar E: Memory in mice as affected by intracerebral puromycin. Science 141:57–59, 1963
12. Barondes SH, Cohen HD: Puromycin effect on successive phases of memory storage. Science 151:594–595, 1966
13. Andry DK, Luttges MW: Memory traces: Experimental separation by cycloheximide and electroconvulsive shock. Science 178:518–520, 1972
14. Flexner LB, Serota FG, Goodman RH: Cycloheximide and acetoxycycloheximide: Inhibition of tyrosine hydroxylase activity and amnestic effects. Proc Natl Acad Sci USA 70: 354–356, 1973
15. Quartermain D, Botwinick CY: Role of the biogenic amines in the reversal of cycloheximide-induced amnesia. J Comp Physiol Psychol 88:386–401, 1975
16. Rutledge LT: Synaptogenesis: Effects of synaptic use, Neural Mechanisms of Learning and Memory. Edited by Rosenzweig MR, Bennett EL. Cambridge, Mass., MIT Press, 1976, pp 329–339
17. Trudell JR: A unitary theory of anesthesia based on lateral phase separations in nerve membranes. ANESTHESIOLOGY 46: 5–10, 1977
18. Sternberg S: High speed scanning in human memory. Science 153: 652–654, 1966
19. Sternberg S: Memory scanning: New findings and current controversies. Q J Exp Psychol 27:1–32, 1975
20. Adam N, Collins GI: Late components of the visual evoked potential to search in short-term memory. Electroencephalogr Clin Neurophysiol 14:147–156, 1978