MEMORY TRACES IN THE BRAIN

DANIEL L. ALKON

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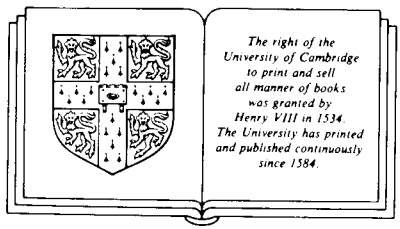
DANIEL L. ALKON, M.D.
Section on Neural Systems,
National Institute of Neurologic
and Communicative Disorders and Stroke
at the Marine Biological Laboratory
Woods Hole, Massachusetts



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Preface

Humans appear, in one important respect, to be no different from other organisms: They seek homeostasis. They strive for equilibrium. This homeostatic orientation is manifest not only by our continual efforts to satisfy obvious biological needs and drives, but by our very human tendency to avoid uncertainty, to seek the familiar. We are comfortable with what we know, disturbed by the new and different, made anxious by the unexpected. We reinforce, attempt to recreate situations, relationships, ideas, and beliefs that we already know from the past. In fact, this is the essence of why learning and memory are so important for understanding and predicting human behavior – we know the past and try to find it in the future by virtue of what we remember.

Avoidance of uncertainty in our system of beliefs is not only an individual process, it is also a collective, a societal phenomenon. Groups to which we belong subscribe to beliefs about themselves, their universe, and pass these beliefs onto their children. Such beliefs must also contribute importantly to our "scientific" knowledge – knowledge that ultimately must be demonstrated and tested and measured.

It is a prime function of science to transcend our need as individuals and groups for certainty – and thereby ultimately arrive at more certainty. If we can suspend our belief systems, we can generate new hypotheses and paradoxically be most ready to abandon these hypotheses in response to observations of phenomena not consistent with our beliefs. If we can live with the anxiety of uncertainty, we can let our minds range free – we can imagine without knowing, we can leap beyond the familiar. If we can live with the anxiety of uncertainty, we can remove the filters from our senses so that we do not discard subtle unanticipated perceptions – so that we can make the most careful, unbiased observations. Then, we can, in fact, learn from our experience and not only as children, but also as mature, even aged adults, modify our views and our behavior.

In the second half of the twentieth century, we arrived at the problems of learning and memory with collective preconceived notions. Mechanisms of learning and memory must occur within our brains, within neural systems of animals. Learning and memory must occur at the junctions between elements of these systems – the synapses. Learning and memory must involve structural changes – growth and formation of new synapses or marked transformations of old neuronal geometry. Memory must become permanent when the neurons make new proteins or different amounts of old proteins.

But must learning and memory occur at the synapse itself or can the crucial information be stored in structures in close proximity to the synapse so that signals crossing the synapse are not changed but are transmitted along proximal structures in a modified form? Must memory involve the synthesis of proteins or are there other biochemical steps that critically determine what information is stored? Do neurons have to actually change their shape, size, and number of junctions with other neurons in order for us to remember? Can we suspend our beliefs to truly ask these questions?

If we can, then we must study the processes themselves. We must study learning and memory as they occur in nature – not as we *think* they occur. Then we must be guided through the jungle of possibilities to the realm of realities, of actualities, by what we can sense, at any moment, in the here and now.

Described here is only one scientific perspective – a picture, sketched and colored of necessity through a haze. This is a picture unavoidably out of focus, relying on the suggested images that emerge from limited bits of information. For me, this picture has an inherent beauty – a beauty, which in its appreciation, offers an opportunity to transcend the very finite concerns of my own survival and well-being. But this picture is not the only one from which I derive intellectual satisfaction, nor is it a picture that has sprung simply from the work of my laboratory or my generation. The beauty of science, luckily, can be shared, and science evolves through this sharing and its transmission from one individual to another. The ultimate sharing of scientific insight provides the global context of all of our individual efforts and shapes our collective understanding.

The focus of this volume on a rather restricted area and mode of inquiry should not convey that its content is in isolation from inquiries of the past or the present. The electrophysiologic techniques and concepts at the center of our studies here were gifts from our predecessors

such as Galvani, Bernstein, Cajal, Katz, Hodgkin, Huxley, Cole, and Eccles. The use of "simple" systems to uncover integrative functions of neural networks was pioneered in the work of Hartline, Kuffler, Wiersma, Tauc, Nicholls to name a few. Our notions as to how "complex" vertebrate systems function derive from, among others, von Bekesy, Eccles, Mountcastle, Hubel, Wiesel, Llinas, Ito, and Anderson.

The possibilities of "simple" systems for the exploration of mechanisms of learning were first understood by Horridge, Bruner, Tauc, and Kandel. Kandel and his colleagues later creatively pursued these possibilities. Parallels among associative learning behaviors of animals of vastly different levels of evolution were revealed by von Frisch, Menzel, Davis, Gelperin, and Sahley. Quantitative analyzable features of associative learning were brilliantly derived by Pavlov and later by Thorndike, Hull, Skinner, Gormezano, Rescorla, Wagner, and many more. In my own laboratory, many contributed to the work described here. These include Bank, Collin, Coulter, Crow, Disterhoft, Farley, Goh, Grossman, Harrigan, Heldman, Kuzirian, Lederhendler, Lo Turco, Naito, Neary, Shoukimous, and Tabata. In the text I mention few names, not because I do not recognize the contributions of these many colleagues, past and present. Rather, it is my attempt to present the science itself, observations and hypotheses. It is the science, data and speculation, rather than the personalities that I hope will take center stage.

Finally, I would like to gratefully acknowledge the encouragement, support, critical judgement, and friendship of Harold Atwood, Lynn Bindman, Robert De Lorenzo, Dori Gormezano, Masao Ito, Rodolfo Llinas, John Pfeiffer, Rami Rahaminoff, Howard Rassmussen, Victor Shashoua, Ladislav Tauc, Nakaakira Tsukahara, Charles Woody, and my wife Betty. To find and maintain the courage of one's convictions and equally important the courage to modify those convictions as experience dictates is necessary for any venture into the unknown. On occasion, most of us have experienced the loneliness, albeit a sometimes splendid loneliness, of asking questions passionately, without compromise. Yet, for me, and I suppose for most, that loneliness is tolerable only because of those with whom we do not feel alone. In this sense, as in the historical sense of the evolution of human thought, no quest, no action, ever entirely resides within one individual.

Woods Hole, 1986

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1
Introduction

How do we remember? What is it that determines our consciousness and colors the nature of our experience? What has preserved the records of our past and is continually recalled in our present and forever shapes our future? Surely this process of recording and recall is at the core of our very essence as human beings.

When we ask how do we remember, we are really asking several interrelated questions. We are asking first how do we sense stimuli in our environment? How is this sensed or perceived information processed to ultimately result in behavior? How are patterns of sensed and behaviorally expressed information stored? And, ultimately, how is stored information subsequently recalled?

There is now abundant evidence that sensation, integration, and behavioral expression is accomplished by our nervous systems. Groups of neurons linked together by synaptic junctions provide complex pathways along which signals triggered by stimulus patterns travel. The exact nature of these pathways and the integrative tasks they perform are clearly understood in only a relatively few number of organisms. (All the figures in this chapter are to be used for impressions of such networks rather than precise details of the pathways.) Even in relatively simple invertebrate species, neural systems have been comprehensively analyzed usually within limited sections. [Examples include the eye of the horseshoe crab *Limulus*, the segmental ganglia of the medicinal leech *Hirudo*, and the interaction of the visual and vestibular pathway of the nudibranch mollusc *Hermissenda crassicornis* (Figure 1).]

In more complex vertebrate species (such as the rabbit, cat, and monkey), pathways have been determined mainly as relationships between stations of neuron clusters or "nuclei." Touch signals from a limb, for example, are transmitted by sensory cells to cells within the spinal cord. Spinal cord cells can send signals back to muscles to execute behavior (Figure 2), can interact with other spinal cord cells to provide

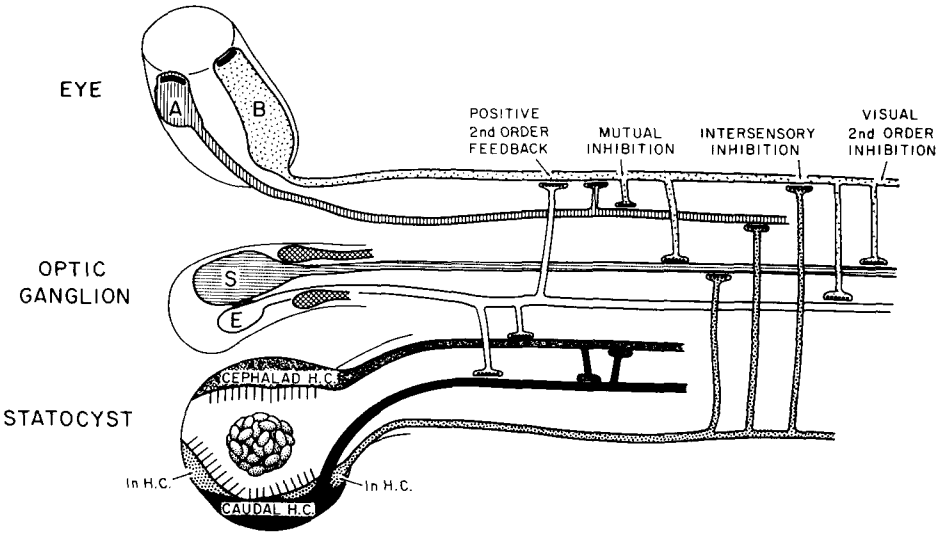

Figure 1. *Hermissenda* neural system (schematic and partial diagram) responsive to light and rotation. Each eye has two type A and three type B photoreceptors; each optic ganglion has 13 second-order visual neurons; each statocyst has 12 hair cells. The neural interactions (intersection of vertical and horizontal processes) identified to be reproducible from preparation-to-preparation are based on intracellular recordings from hundreds of pre- and postsynaptic neuron pairs. In HC, hair cell ~ 45° lateral to the caudal north–south equatorial pole of statocyst; S, silent optic ganglion cell, electrically coupled to the E cell; E, optic ganglion cell, presynaptic source of EPSPs in type B photoreceptors. The E second-order visual neuron causes EPSPs in type B photoreceptors and cephalad hair cells and simultaneous inhibitory postsynaptic potentials (IPSPs) in caudal hair cells. (From Alkon, 1980)

local integrative functions, or can relay information to nuclei within the brain, which in turn relay information to still other nuclei for further processing (Figure 3). We also know many details about the organization of functional units within particular brain regions. For example, within the vertebrate retina the sensory cells, called rods and cones, send signals to other cells, called bipolar and horizontal cells, which in turn communicate with amacrine and ganglion cells (Figure 4), which finally relay information to more central neural clusters or nuclei of the brain (including the lateral geniculate, superior colliculus) and, ultimately, the visual cortex (Figure 5). Similar knowledge has been accumulated about functional units within the hippocampus and the cerebellum (Figures 6 and 7). Despite this large body of accumulated knowledge of neural organization, however, we are still very far from being able to precisely describe exactly how signals flow along discrete neuronal pathways to

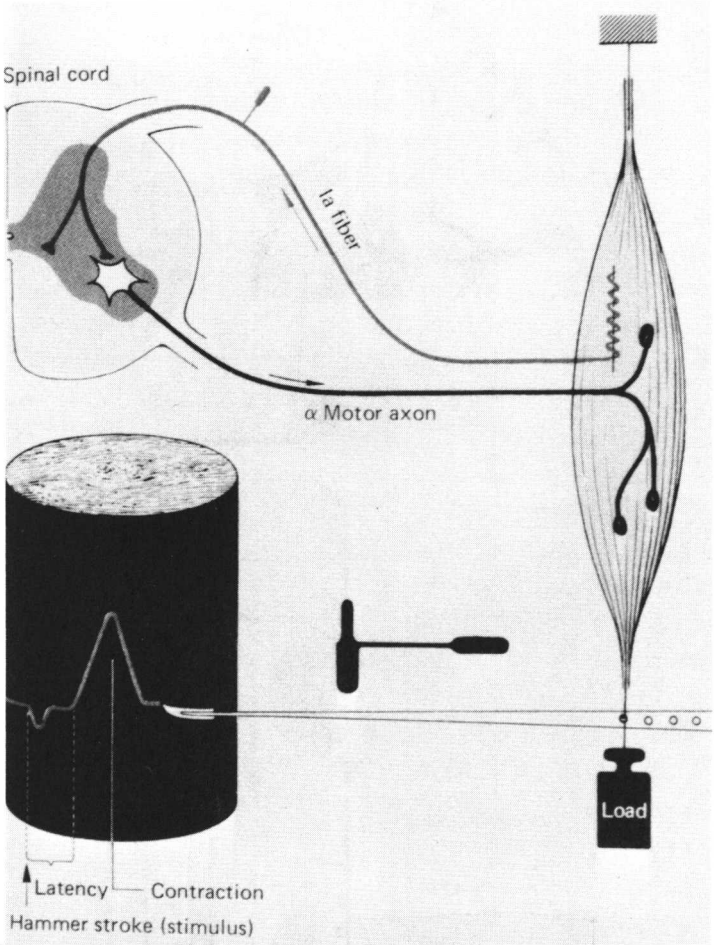

Figure 2. Reflex arc of the monosynaptic stretch reflex. A light step, with a hammer on the stylus recording muscle length (downward deflection of the trace on the recording paper) after a brief latency, produces contraction of the muscle. The reflex arc underlying this response is diagrammed, from the muscle spindles via the Ia fibers to the motorneurons and back to the muscle. (From Schmidt et al., 1978)

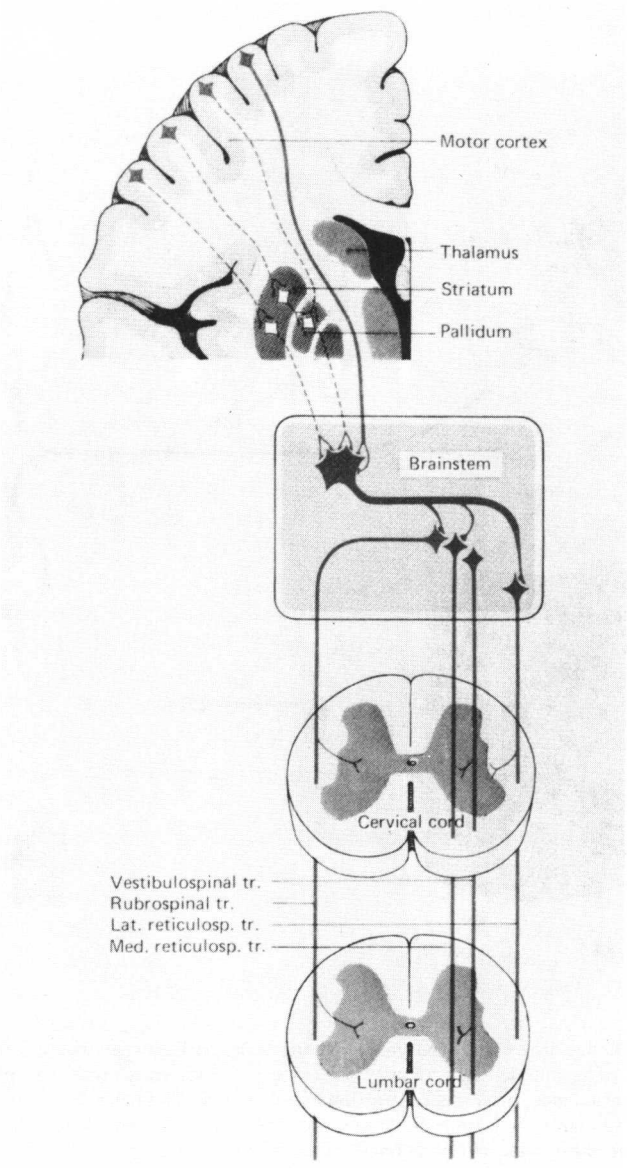

Figure 3. Schematic diagram of the courses of the most important extrapyramidal tracts from the supraspinal motor centers into the spinal cord. The neuron with a thick axon in the brainstem symbolizes the crossing of most of the extrapyramidal motor fibers to the opposite side at that level, and does not imply convergence. The pathways from motor cortex to basal nuclei are partly collaterals of the corticospinal tract and partly separate efferents. The details of connectivity among the brainstem structures involved in motor activity are extremely complicated; the representation here is greatly simplified. (From Schmidt et al., 1978)

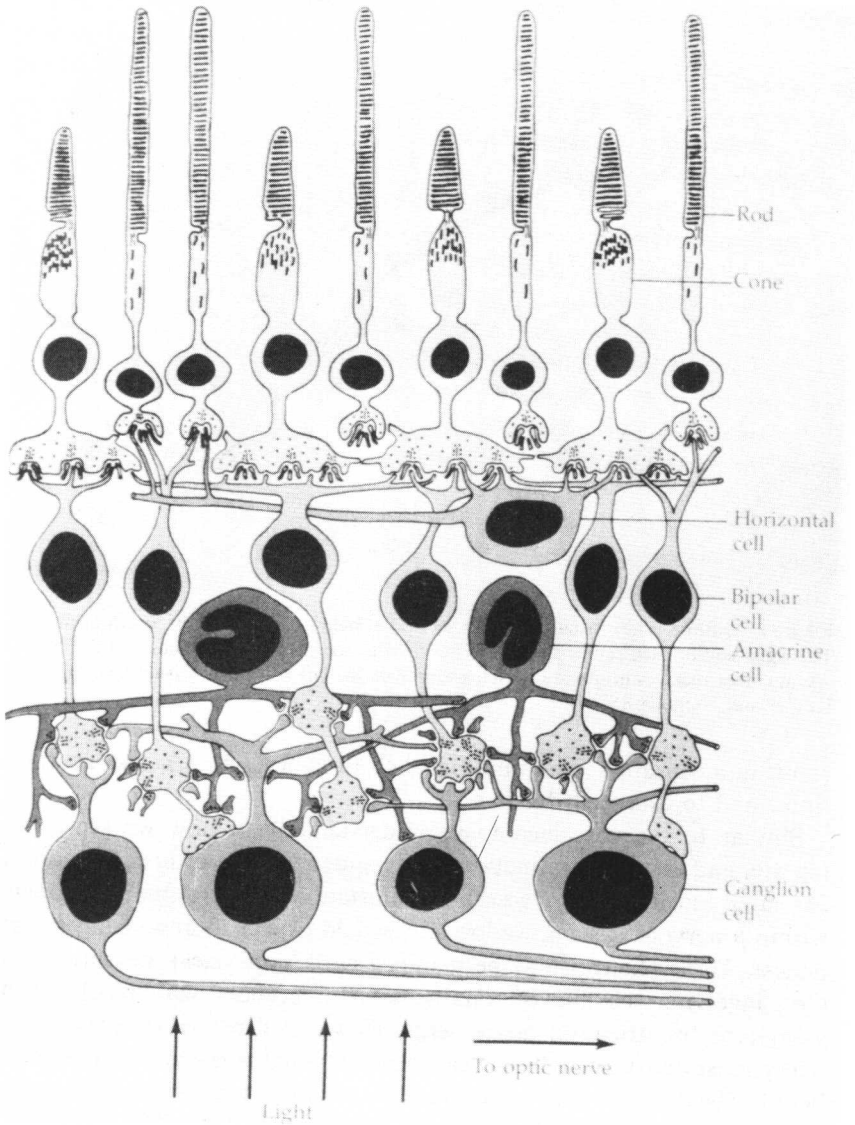

Figure 4. Organization of primate retina, after Dowling and Boycott (1966). (From Kuffler and Nicholls, 1977)

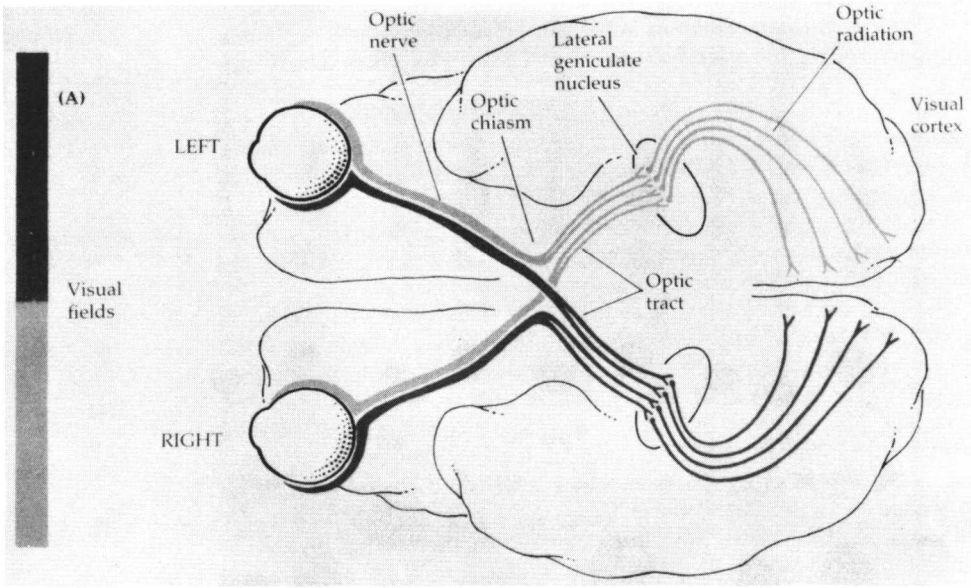

Figure 5. Outline of the visual pathways seen from below (base of the brain) in primates. The right side of each retina projects to the right lateral geniculate nucleus and the right visual cortex receives information exclusively from the left half of the visual field. (From Kuffler and Nicholls, 1977)

result in a sensation or an image, to afford choices, to generate abstractions, and to execute behaviors.

Similar to the very incomplete understanding of how we sense, integrate, and express information is our understanding of how we store it for later recall. When we seek manifestations of information storage within a nervous system, we logically would expect to find changes that persist. These changes may be manifest with biophysical measurements (i.e., involving the flux of ions across membranes), with biochemical assays, or by structural assessments. However they are manifest, they really must constitute a biological record of what is learned and remembered. These learning-induced changes are what remain long after the original stimulus patterns that produced them are gone. These changes, be they biophysical, biochemical, and/or structural are what give memory its physical reality.

How do we find them? And how do we reconstruct the process by which they occur? In the best of all possible worlds, we would trace the

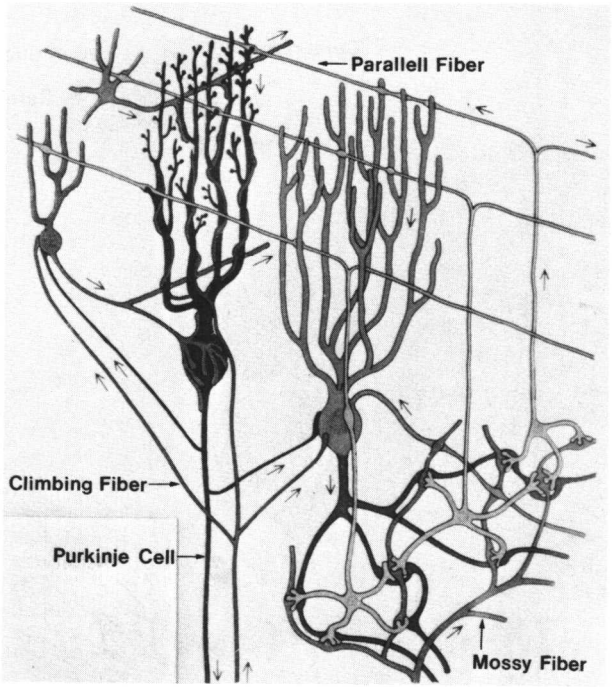

Figure 6. Interconnection of neurons in the cortex follows an elaborate but sterotypic pattern. Each Purkinje cell is associated with a single climbing fiber and forms many synaptic junctions with it. The climbing fiber also branches to the basket cells and Golgi cells. Mossy fibers come in contact with the terminal "claws" of granule-cell dendrites in a structure called a cerebellar glomerulus. The axons of the granule cells ascend to the molecular layer, where they bifurcate to form parallel fibers. Each parallel fiber comes in contact with many Purkinje cells, but usually it forms only one synapse with each cell. The stellate cells connect the parallel fibers with the dendrites of the Purkinje cell, the basket cells mainly with the Purkinje-cell soma. Most Golgi-cell dendrites form junctions with the parallel fibers but some join the mossy fibers; Golgi-cell axons terminate at the cerebellar glomeruli. Cells are identified in the key at lower left; arrows indicate direction of nerve conduction. (From Llinas, 1975)

information as it entered the nervous system (i.e., at the input stage); we would follow it as it coursed through all the integrative steps. Through neural pathways, we would watch the progressive transformations at critical sites within the pathways, and we would determine how these transformations altered information that exited the nervous system (i.e., at the output stage). The impracticality of even approximating such an analysis in a vertebrate nervous system, as suggested above, is over-

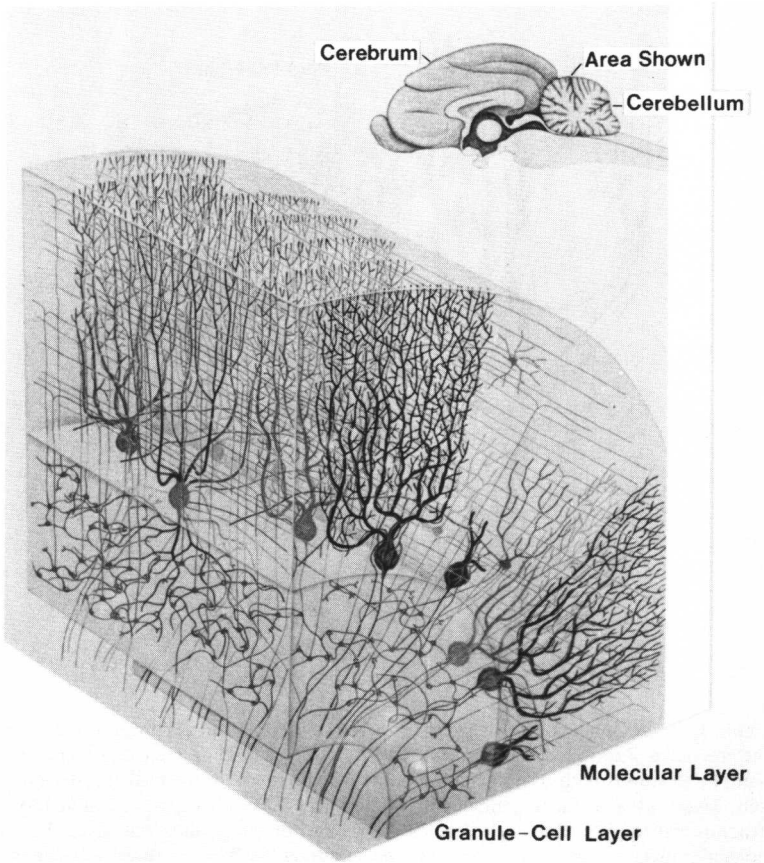

Figure 7. Architecture of the cortex of the cerebellum is diagrammed for a section of tissue from the brain of a cat. The location of the tissue section is indicated in the drawing at the top right; the same array of cells is repeated throughout the cortex. The cortex is organized around the Purkinje cells, whose somas, or cell bodies, define the border between the superficial molecular layer and the deeper granule-cell layer. In the molecular layer are the Purkinje-cell dendrites, which are arrayed in flattened networks like pressed leaves, and the parallel fibers, which pass through the dendrites perpendicularly. This layer also contains the stellate cells and the basket cells, which have similarly flattened arrays of dendrites. In the deeper layer are the granule cells, which give rise to the parallel fibers, and the Golgi cells, which are characterized by a cylindrical dendritic array. Input to the cortex is through the climbing fibers and mossy fibers; output is through the axons of Purkinje cells. (From Llinas, 1975)

whelming. Yet it is in the vertebrate nervous system, more particularly a mammalian nervous system, and to be precise the human nervous system, in which we wish to uncover the physical reality of memory.

Confronted with this dilemma, scientists over the last several decades developed several major experimental strategies. One strategy involved the use of lesions–ablations of critical brain areas to eliminate what might be a site essential for the storage of a particular memory. This approach was reinforced by a clinical strategy that depended on the pathologic examination of human brains to search for natural lesions that might account for memory deficits previously demonstrated in living patients. Clinicians for many generations made such observations, accumulating experience with a variety of pathologic lesions associated with a variety of clinical syndromes.

With the introduction of electrophysiologic techniques, new possibilities emerged. Microelectrodes could be placed in well-specified brain regions during surgery and used to inject very small amounts of current that might elicit memories. Patients in a conscious state and without pain were able to communicate remembrance of past experience in response to the microelectrode stimulation. More promising were the extracellular potentials that could be recorded and amplified by electrodes inserted into the brains of vertebrate species during the acquisition and retention of learning. Workers monitored changes of extracellularly recorded electrical activity (i.e., activity recorded outside of cells) as they were correlated with learning. Lesion studies were often coupled with recording measurements in efforts to localize memory storage sites.

Despite these efforts and these advances, because of the complexity of the vertebrate brain, mapping the involved neural circuits and their learning-induced modification has proved formidable and, to a considerable degree, elusive, although some very promising results have just recently become available (see Chapter 15).

Another research strategy involved biochemical intervention and measurements. This work at first centered largely on manipulations concerning protein synthesis. Animals given learning tasks were found to have differences in RNA metabolism, and inhibition of protein synthesis disrupted the retention of learned behavior. Later pharmacologic manipulations of neurotransmitter substances (which carry signals across synaptic junctions between neurons) and hormonal agents were shown to affect learning. Still elusive, however, were the critical mechanisms and local sites whereby such manipulations caused their effects. It was never clear, for instance, whether a change in protein synthesis was a cause or

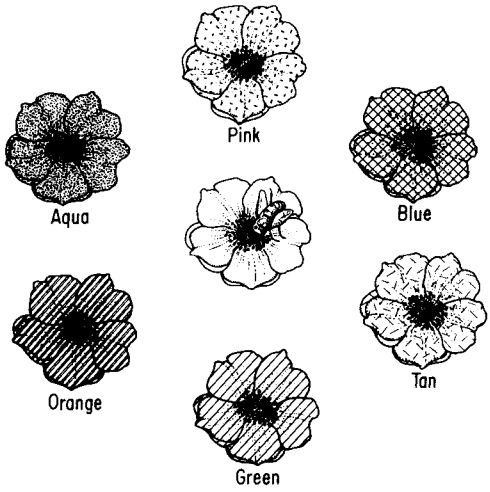

Figure 8. Bees learn to associate the color of a flower with food. (From Menzel and Erber, 1978)

an effect of learning, whether such a change actually stored information or simply passively reflected such storage elsewhere within the brain, and frequently, whether or not such changes also represented part of sensory, integrative, or motor physiology not at all unique to learning.

Still another strategy involved the use of learning in less evolved species as models for our own learning capacity. It was hoped that enough might be common to learning of simple and more complex animals that cellular insights in the former would have relevance for the latter. Among the earliest preparations, which are still useful today, were the locust and grasshopper, bees (Figure 8), and gastropod molluscs more familiar to us as snails. With these preparations, it was thought possible to combine electrophysiologic and biochemical analyses to arrive at complete descriptions of neural circuits and to localize the actual mechanisms for storage and recall of learned information that bore resemblance to, or shared features with, that which we know in our own conscious experience.

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