

THE CORTEX OF THE CEREBELLUM

In this part of the brain the pattern of connections between nerve cells has been determined in detail. The pattern is now understood well enough to relate it to the function of the neuronal networks

by Rodolfo R. Llinás

In the study of the brain a perennial goal is to infer function from structure, to relate the behavior of an animal to the form and organization of the cells in its central nervous system. At the highest level this task can be equated with the tantalizing problem of identifying the mind with the brain, a problem whose solution may well elude us for some time to come. On a more modest scale the operation of certain limited regions of the brain can already be interpreted in terms of cellular anatomy. For example, the sensory nerve circuits associated with the retina of the eye and the olfactory organs of the nasal cavity have been traced in detail, and our understanding of these circuits has helped to reveal how visual and olfactory information is processed.

The region of the brain where the correlation of anatomy with function has been determined with the greatest success is the cortex, or outer sheath, of the cerebellum. The cells of this structure have been classified according to their form and their position and orientation in the tissue. The properties of each kind of cell, and in particular their response to stimulation, have been investigated. Perhaps most important, a complete "wiring diagram" of the cerebellar nerve circuit has been drawn, showing how the several types of cells are interconnected. From this knowledge of the individual cell and of the pattern of connections between cells one can begin to predict the behavior of the system as a whole.

Of course, our knowledge of the cerebellum is far from complete. To begin with, a comprehensive explanation of the cerebellum would require an equally comprehensive understanding of other parts of the brain with which the cerebellum communicates; some of those

areas remain quite mysterious. Furthermore, our present model of the cerebellum is best suited to describing what happens when a single nerve impulse enters the cortex, and it must be somewhat vague in specifying the effect of a complex pattern of impulses. The model is valuable nevertheless; at the least it offers evidence that the functioning of the brain can be explained simply as the sum of the activities of its component cells, that in the final analysis all mental activity consists of known kinds of interactions between known kinds of nerve cells.

Anatomy of the Cerebellum

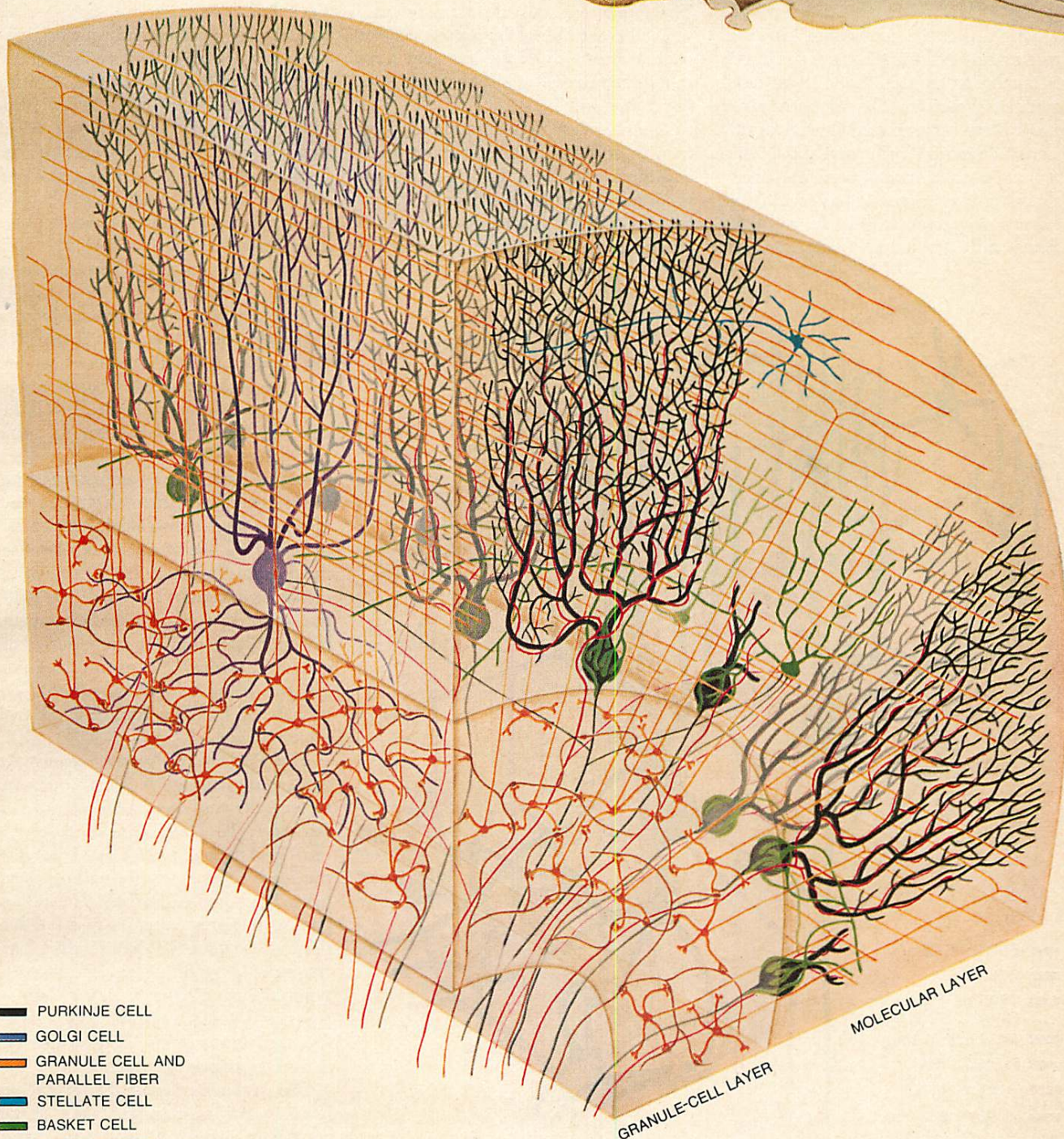
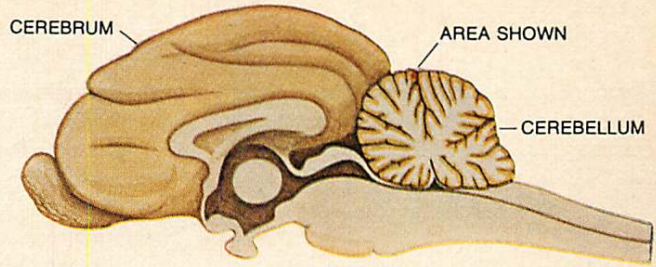
The cerebellum lies at the back of the skull behind the brain stem and under the great hemispheres of the cerebrum. Its name is a Latin diminutive of "cerebrum" and means simply "lesser brain." Superficially that is an adequate description of the cerebellum: it is much smaller than the cerebrum but shares certain morphological features with it. As in the cerebrum, the highest functions in the cerebellum are confined to the thin layer of gray matter that makes up the cortex and, as in the cerebrum, this layer is elaborately folded and wrinkled to increase its area. The folds are in fact much deeper and more closely spaced than those of the cerebral cortex. If the cerebellum is split down the middle, the folds form a pattern that resembles a tree, which medieval anatomists termed the *arbor vitae*, or tree of life [see illustrations on page 59].

Both the structure and the function of the cerebellum have been known, at least in terms of broad principles, since the end of the 19th century. The challenge to modern investigators has been in combining the two kinds of data and

discovering how a particular structure generates the observed behavior.

The fundamentals of cerebellar anatomy were established in 1888 by Santiago Ramón y Cajal of Spain. He employed a staining technique that had been developed in 1873 by Camillo Golgi of Italy, in which the tissue is impregnated with salts of silver, coloring some of the nerve cells deep brown or black. By studying many stained sections of tissue Ramón y Cajal identified the principal neurons, or nerve cells, of the cerebellar cortex and described their arrangement in space. The arrangement itself is remarkable: some elements of the system are arrayed at right angles to others with extraordinary precision and delicacy. Finally, Ramón y Cajal determined the nature of the connections between the neurons and recognized in them a stereotyped pattern, repeated throughout the cortex. The essential accuracy of his observations has been repeatedly confirmed, and the neuronal circuit he described has been found to be a universal feature of the cerebellum from the most primitive vertebrates to the most advanced.

The first reliable clue to the function of the cerebellum was provided by the Italian physiologist Luigi Luciani, who discovered that experimental animals deprived of a cerebellum suffer disturbances of coordination and equilibrium. Other investigators subsequently demonstrated that the cerebellum communicates with both the motor centers of the cerebrum and the proprioceptive organs of the body, the nerves that sense the relative position and tension of the muscles. By the end of the 19th century the English physiologist Charles Sherrington was able to conclude that the cerebellum coordinates the movements of the muscles but does not initiate them. Although



- PURKINJE CELL
- GOLGI CELL
- GRANULE CELL AND PARALLEL FIBER
- STELLATE CELL
- BASKET CELL
- CLIMBING FIBER
- MOSSY FIBER

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 top right; the same array of cells is repeated throughout the cortex. Each cell type is identified by color in the key at bottom left. 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.

Sherrington's formulation can no longer be accepted entirely, it has been refined rather than refuted [see "The Cerebellum," by Ray S. Snider; SCIENTIFIC AMERICAN, August, 1958].

The Cerebellar Neurons

One reason the cerebellum is so well understood today is that its organization is much simpler than that of most other parts of the brain. The basic circuit of the cortex—with few modifications the circuit described by Ramón y Cajal—involves just seven nerve elements. Two of them conduct nerve impulses into the cortex; they are called the climbing fibers and the mossy fibers. Another

serves as the sole output of the system; it is the Purkinje-cell axon. The four remaining nerve elements are the granule cells, the Golgi cells, the basket cells and the stellate cells; they are entirely indigenous to the cerebellar cortex and run short distances between the other cells. The input terminals are often referred to as afferent fibers, the output cells as efferent neurons and the cells that serve as intermediaries as interneurons [see illustration below].

The discovery of a third afferent system, in addition to the climbing fibers and the mossy fibers, has recently been reported by F. E. Bloom and his colleagues at Saint Elizabeths Hospital in Washington. It consists of fibers arising

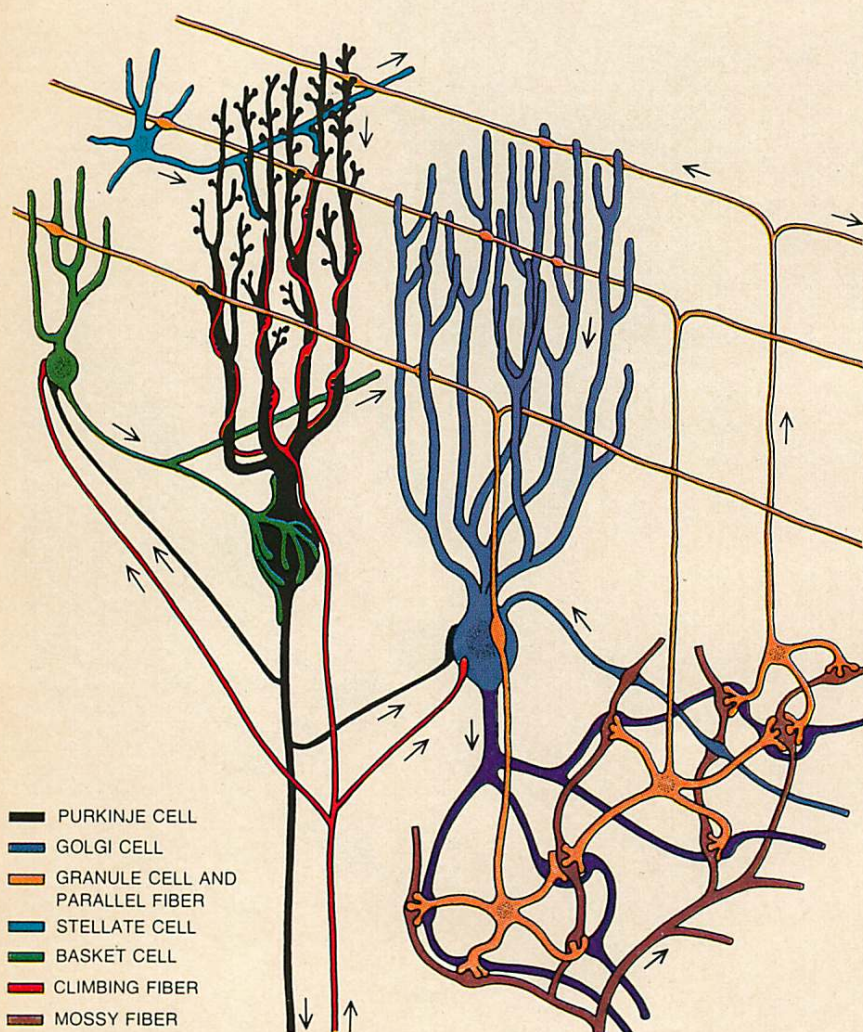
from a structure in the brain stem called the locus ceruleus. Because it is not yet clear how this system is related to the other functions of the cerebellum it will not be considered further here.

Neurons are diverse in form, but they all have certain structures in common. Each has a soma, or cell body, which contains the nucleus and usually a major portion of the cytoplasm as well. Extending from the soma are the dendrites (from the Greek for "tree"), which often branch repeatedly, and the axon, which can be quite long and may or may not branch. For the most part dendrites conduct nerve impulses toward the body of the cell and the axon conducts impulses away from it. The junction where the axon of one cell meets a dendrite of another is a synapse.

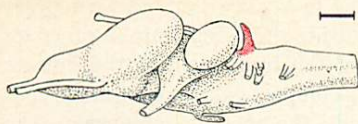
When a nerve impulse reaches the terminal point of the axon, it provokes the release of a transmitter substance, which passes across the synapse and alters the membrane of the dendrite of the next cell in the neural pathway, changing its permeability to certain ions. The resulting flow of ions across the membrane generates a small electric current, which propagates as a local electrical disturbance of the membrane down the dendrite to the soma. If the stimulating neuron is excitatory, and if the stimulation exceeds a threshold, the receiving cell will "fire" and the impulse will be conveyed through the axon to the next synapse. If the first cell is inhibitory, the probability that the receiving cell will fire is reduced.

The Purkinje cells were among the first neurons recognized in the nervous system; they are named for Johannes E. Purkinje, the Czech physiologist who described them in 1837. They are among the most complex of all neurons. Each has a large and extensive dendritic apparatus referring impulses to a bulblike soma, and a long, slender axon [see illustration on page 60]. The dendrites of a typical human Purkinje cell may form as many as 100,000 synapses with afferent fibers, more than those of any other cell in the central nervous system.

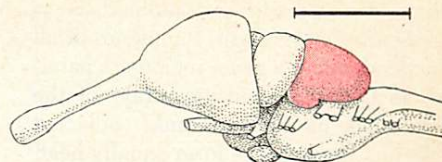
The Purkinje cells are the pivotal element in the neuronal network of the cerebellar cortex. They are found throughout the cortex, their cell bodies constituting a continuous sheath called the Purkinje-cell layer. The dendrites extend densely above the Purkinje-cell layer, toward the boundary of the cortex; this region is called the molecular layer. The axons extend in the opposite direction, into the deeper portion of the cortex called the granule-cell layer. The axons, in fact, penetrate far beyond this



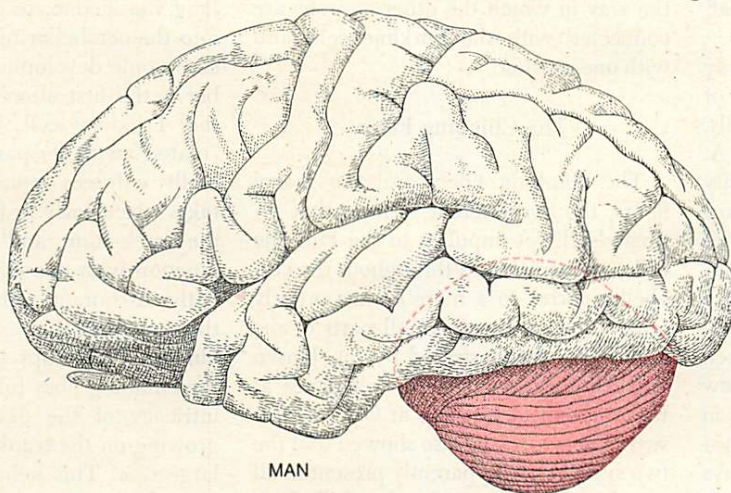
INTERCONNECTION OF NEURONS in the cortex follows an elaborate but stereotyped pattern. Each Purkinje cell is associated with a single climbing fiber and forms many synaptic junctions with it. The climbing fiber also branches to the basket cells and Golgi cells. Mossy fibers come in contact with the terminal "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.



FROG



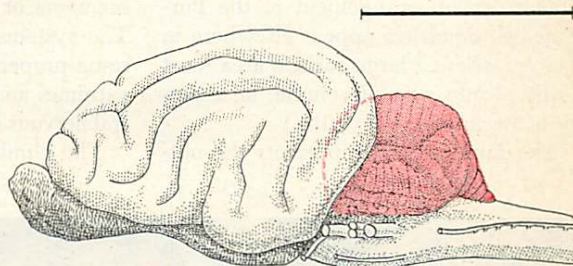
ALLIGATOR



MAN



GOOSE



CAT

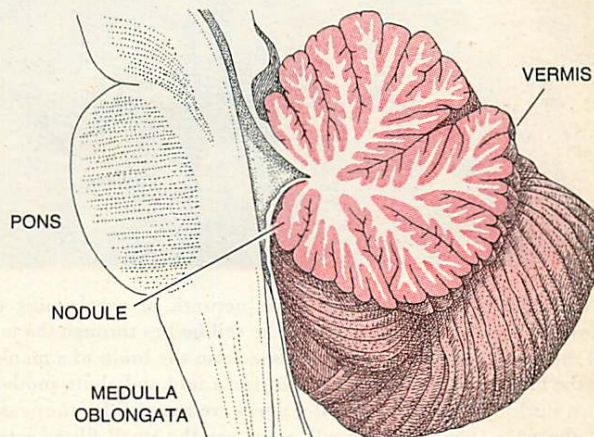
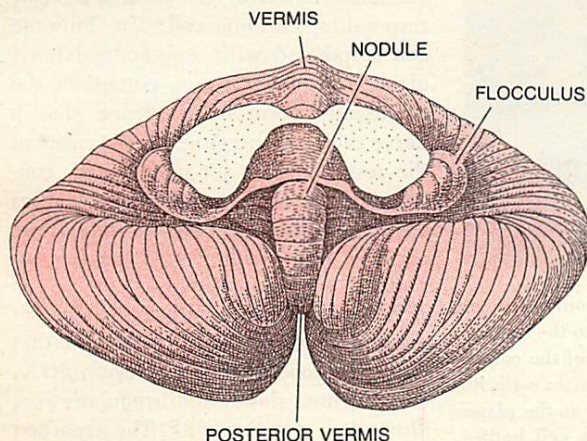
EVOLUTION OF THE CEREBELLUM suggests that its function has become more important during the span of vertebrate history. From the amphibians through the reptiles and birds to the mammals it has become progressively larger, both in actual mass and

in proportion to overall brain size. It has also become more convoluted, providing a greater area of cortex. In man it is a large and deeply fissured structure. The cerebellums are shown in color; the scale in relation to the human brain is indicated by horizontal bars.

region; they pass out of the cortex entirely, through the white matter in the core of the cerebellum, and eventually reach isolated lumps of gray matter called cerebellar nuclei. The nuclei are also supplied with side branches of the climbing-fiber and mossy-fiber input

systems, so that they receive all the information going to the cortex. In the nuclei the incoming messages are blended with those returning from the cortex and are relayed to other parts of the brain and down the spinal cord to the rest of the body.

The dendrites of the Purkinje cells have an unusual arrangement that is at once the most conspicuous structural element in the cerebellar cortex and an important clue to its functioning. The entire mass of tangled, repeatedly bifurcating branches is confined to a single



HUMAN CEREBELLUM consists of two hemispheres separated by a narrow girdle, the vermis. At left it is viewed from below; the brain stem has been removed to reveal the vermis, flocculus and

nodule, which are involved in eye movement, among other functions. At right the cerebellum is sectioned through the vermis. The pattern of cortical folds is called the *arbor vitae* ("tree of life").

plane, as if it had been flattened like a pressed leaf. Moreover, the planes of all the dendrites in a given region are parallel, so that the dendritic arrays of the cells stack up in neat ranks; adjacent cells in a single plane form equally neat, but overlapping, files.

To a large extent this orderly array determines the nature and number of contacts made with other kinds of cells. As has been pointed out by Clement A. Fox of the Wayne State University School of Medicine, the dendrites are organized like a net to "catch" as many incoming signals as possible. Fibers running perpendicular to the plane of the dendrites will intersect a great many Purkinje cells, although they will touch each cell only once or at most a few times. Fibers oriented in this way do in fact constitute one of the afferent systems in the cortex. (Geometric arrays similar to the arrangement of the Purkinje-cell dendrites appear elsewhere in biology where a large surface area must be fitted into a small volume; an example is the antennae of moths.)

The Purkinje cell represents the out-

put system of the cerebellar cortex, but it is not a mere transmitter or repeater of information originating elsewhere. It is part of an indivisible system of neurons whose activity is determined entirely by the way in which the other neurons are connected with the Purkinje cells and with one another.

The Climbing Fiber

The climbing fibers and the mossy fibers, the two afferent systems that ultimately direct impulses to the Purkinje cells, are distributed throughout the cerebellar cortex in a more or less orderly array. Their presence in all parts of the cortex was demonstrated by Jan Jansen and Alf Brodal and their colleagues at the Anatomical Institute at Oslo in Norway. These workers also showed that the two systems are apparently present in all members of the vertebrate subphylum. The systems are radically different; in some properties they represent opposite extremes among the neurons of the central nervous system.

The climbing fiber is virtually a pri-

vate line to a given Purkinje cell. It begins outside the cerebellum in other regions of the brain such as the inferior olive, a compact collection of nerve cells alongside the medulla oblongata. The long, ramified axons of these cells extend into the cerebellar nuclei and cortex. In embryonic development the *climbing fiber* is the first afferent system to reach the Purkinje cell, and once it has "mated" with its particular cell it generally enforces monogamy. The union takes place early in the development of the cerebellum, and the formation of a junction with one climbing fiber apparently discourages others from attaching themselves to the same cell. As the Purkinje cell develops its net of dendrites the climbing fiber follows, matching the intricacy of the dendrites like a vine growing on the trunk and branches of a large tree. This behavior is the root of its name.

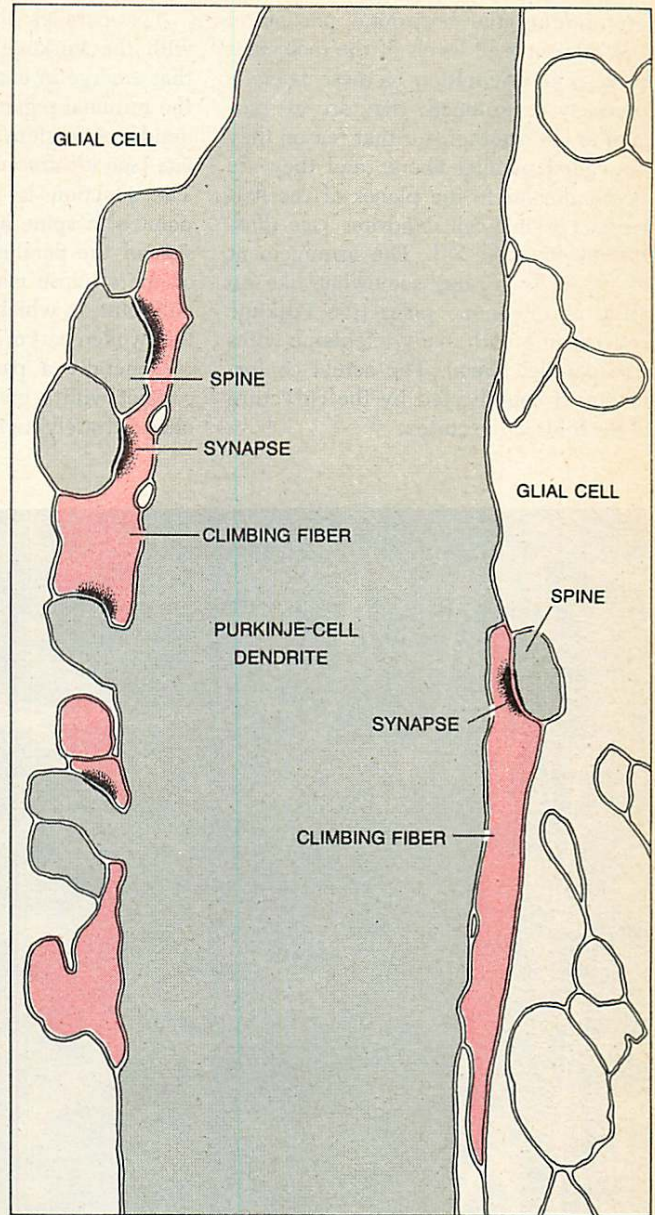
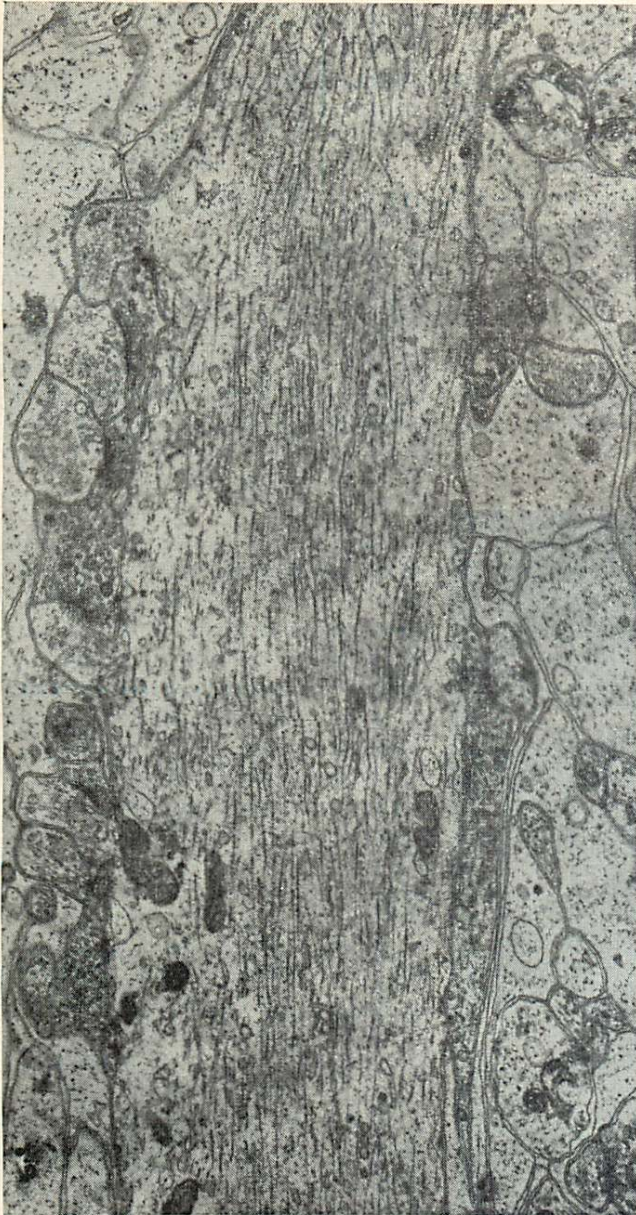
It was once believed the climbing fiber formed synapses with the smooth surface of the Purkinje-cell dendrites. It has now been demonstrated by Luis M. H. Larramendi and his colleagues at the University of Chicago, however, that the two cells are actually in contact only where small spines protrude in groups from the surface of the Purkinje-cell dendrite [see illustrations on opposite page]. There are many such spines on any one Purkinje cell. Dean E. Hillman of the University of Iowa has estimated that a Purkinje cell and its climbing fiber are probably in synaptic contact at about 300 points, which is a large number of junctions to be established between a cell and a single afferent fiber.

The action of the climbing fiber on the Purkinje cell was described in 1964 by John C. Eccles, K. Sasaki and me. Working at the Australian National University in Canberra, we found that stimulating a climbing fiber produced an exceedingly powerful excitation of the corresponding Purkinje cell. The Purkinje cell responded with a prolonged burst of high-frequency action potentials, the electrically recorded evidence that a nerve cell is discharging. The intensity of the response was not unexpected, considering the large number of synapses connecting the cells. The excitation was capable of overriding any ongoing activity in the Purkinje cell.

Recordings made with electrodes implanted in Purkinje cells showed that the action potential arises very quickly, then declines slowly and irregularly [see illustration on page 62]. The recorded pattern represents the firing of the cell body of the neuron and the generation of



PURKINJE CELLS sprout a dense network of overlapping dendrites, all confined to a single plane and extending above the cell bodies through the molecular layer to the surface of the cortex. In this section of tissue from the brain of a monkey the surface of the cortex is the bright diagonal strip; it is inside a fold and abuts another part of the cortex with its own Purkinje cells. The parallel fibers are not visible; they run perpendicular to the plane of the page. The Purkinje-cell axons are the small fibers extending from the cell bodies toward deeper strata. The tissue was prepared by staining it with silver salts; the photomicrograph was made by Clement A. Fox of the Wayne State University School of Medicine.



CLIMBING FIBER forms numerous synaptic junctions with a Purkinje-cell dendrite through spines that protrude in clusters from the surface of the dendrite. The structures visible in the electron micrograph at left are diagrammed and identified in the drawing at right. The several regions labeled "Climbing fiber" are

segments of a single fiber that is wrapped around the dendrite. Nerve impulses are transmitted from the climbing fiber to the dendrite. Glial cells surrounding the synapse are not neurons but serve as a matrix in which the nerve cells are embedded. The photomicrograph was made by Dean E. Hillman of the University of Iowa.

many lesser action potentials in the dendrites as the cell is showered with synaptic transmitters released at many points by the climbing fiber. Because the response is provoked by a single impulse in a single afferent fiber, it is an all-or-nothing phenomenon, that is, it is present in full force or is absent altogether.

The Mossy Fiber

Whereas the climbing fiber generates many connections to a single Purkinje cell, the mossy fiber ultimately excites many Purkinje cells, but through only a few contacts with each of them. Among

all the neurons of the central nervous system, the mossy fiber stimulates one of the largest numbers of cells to be activated by a single efferent fiber.

The mossy fibers do not terminate directly on Purkinje cells, as the climbing fibers do, but on small interneurons, the granule cells, which lie immediately under the Purkinje-cell layer. The granule cells serve as intermediaries, greatly increasing the number of Purkinje cells stimulated by a single afferent fiber.

One reason the granule cells can intersect so many Purkinje cells is that the granule cells are themselves exceedingly numerous. Valentino Braitenberg of the

Max Planck Institute for Biological Cybernetics in Tübingen has calculated that the number of granule cells in the human cerebellar cortex may be 10 times greater than the number of cells previously believed to make up the entire brain. Sanford L. Palay of the Harvard Medical School has commented: "Of the 10^{10} cells in the brain, 10^{11} are in the granular layer of the cerebellar cortex!"

The axon of the granule cell projects upward, past the Purkinje-cell layer and into the molecular layer. There it splits, the two branches taking diametrically opposite directions, so that the axon assumes the form of a capital *T*. Fibers

representing the horizontal portion of the *T* occupy all levels of the molecular layer. The orientation of these fibers is precisely determined: they are all parallel to one another (for that reason they are called parallel fibers), and they are perpendicular to the planes of the flattened Purkinje-cell dendrites [see illustration on page 57]. The arrangement of the cells is thus somewhat like an array of telephone poles (the Purkinje cells) strung with many telephone wires (the parallel fibers). The actual conformation is complicated by the curvature of the folds in the cortex.

The parallel fibers come in contact with the Purkinje cells through spines that emerge in enormous numbers from the terminal regions of the Purkinje-cell dendrites, regions called spiny branchlets [see illustrations on opposite page]. The junction is formed between the point of a spine and a globular expansion of the parallel fiber; the geometry of the synapse may resemble that of a ball joint, in which the spine penetrates the swollen part of the fiber.

Generally a parallel fiber comes in contact with a given Purkinje cell only once or (rarely) twice; nevertheless, most

of the inputs to the Purkinje cells are through the parallel fibers. As I have noted, a single human Purkinje cell can receive as many as 100,000 parallel fibers (compared with a single climbing fiber).

Eccles, Sasaki and I have studied the effects of stimulating the mossy fibers. Like the climbing fiber, the mossy fiber is excitatory, and so is the granule cell it stimulates. Both afferent systems can therefore excite activity in the cerebellar cortex. The influence of the mossy fibers, however, is for obvious reasons diffuse and complex, in contrast to the sharply focused effect of the climbing fiber.

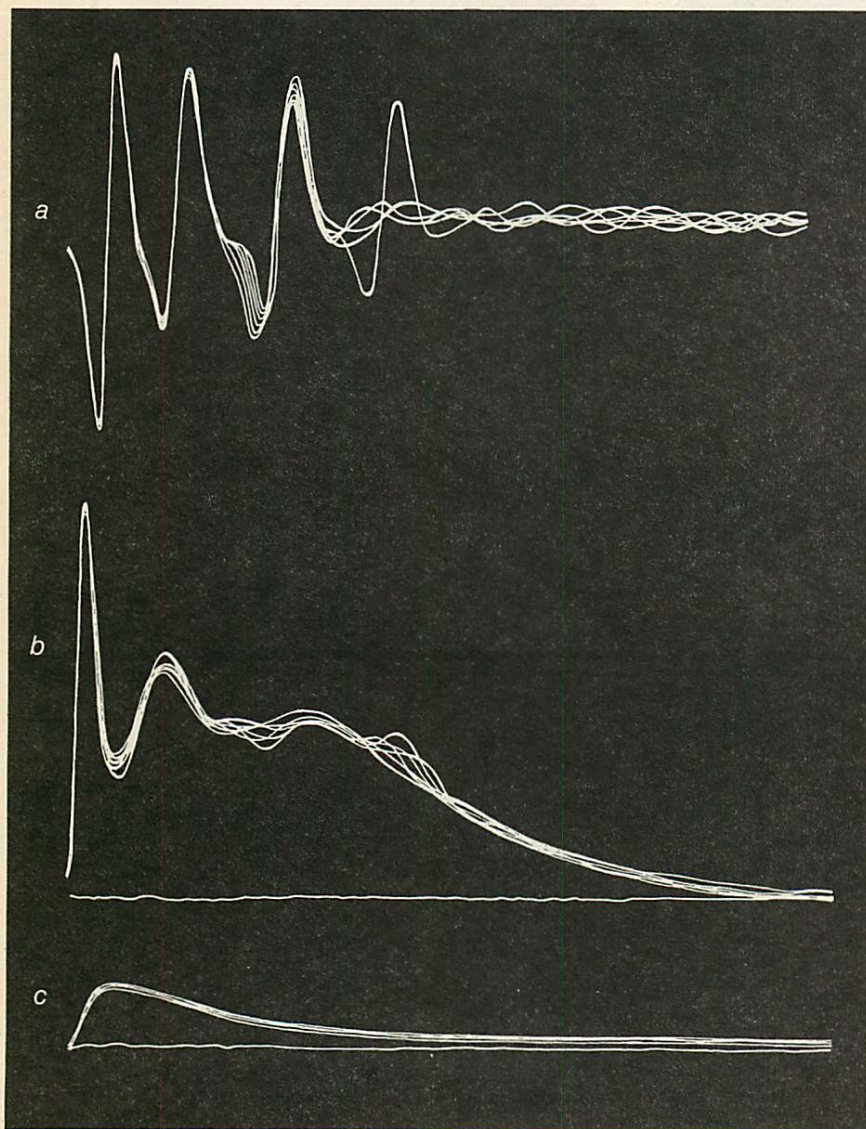
The Interneurons

Embedded in the matrix of the cerebellar circuitry are two sets of interneurons that, unlike the granule cells, have only short axons. One set is located in the molecular layer and consists of basket cells and stellate cells; the other is in the granule-cell layer and is represented by Golgi cells.

The basket and stellate cells are similar and can be considered members of a single class. Both receive impulses from the parallel fibers and act, through their axons, on Purkinje cells. The principal difference between the two types is that the basket cell establishes synaptic junctions with the Purkinje cell in the lower dendrites and on the soma, whereas the stellate cell is more or less confined to the dendrites. Perhaps the most significant anatomical observation on the basket and stellate cells pertains to the spatial distribution of their axons. They are perpendicular to the parallel fibers and are also perpendicular to the axis of the Purkinje cells. The network of cells in the molecular layer thus consists of three basic types of cell process all of which are mutually perpendicular.

In the granule-cell layer the remaining interneuron, the Golgi cell, also receives impulses from the parallel fibers, but its dendrites form synapses directly with the mossy fibers as well. The Golgi cells are components of a specialized synaptic linkage known as the cerebellar glomerulus, which is the basic functional unit of the granule-cell layer. It consists of a bulge or swelling in a mossy fiber, surrounded by the dendrites of granule cells, which in turn are surrounded by the axons of Golgi cells [see illustrations on page 64].

All three kinds of interneuron have been demonstrated to be inhibitory. The inhibitory effect of the basket cell on the soma of the Purkinje cell was initially shown by P. Andersen, Eccles and P. E.



RESPONSE OF A PURKINJE CELL to stimulation by a climbing fiber is recorded electrically. Action potentials (voltages developed across the cell membrane) are measured from outside the cell (*a*) and from inside it (*b*). The response is strong and consistent; several repetitions are superposed here, revealing only small variations. It is an all-or-nothing response; if the climbing fiber fails to fire, only a straight line is recorded. Climbing-fiber stimulation provokes the firing of the Purkinje cell by depolarizing the cell membrane; the phenomenon can be recorded in isolation (*c*) in a damaged cell. The time span of the recordings is about 20 milliseconds. The voltages are not drawn to the same scale; those measured inside the cell (*b*, *c*) are actually many times larger than those measured outside (*a*).

Voorhoeve at the Australian National University in 1963; the inhibition of Purkinje-cell dendrites by stellate cells and the inhibition of granule cells by Golgi cells were demonstrated soon afterward by Eccles, Sasaki and me.

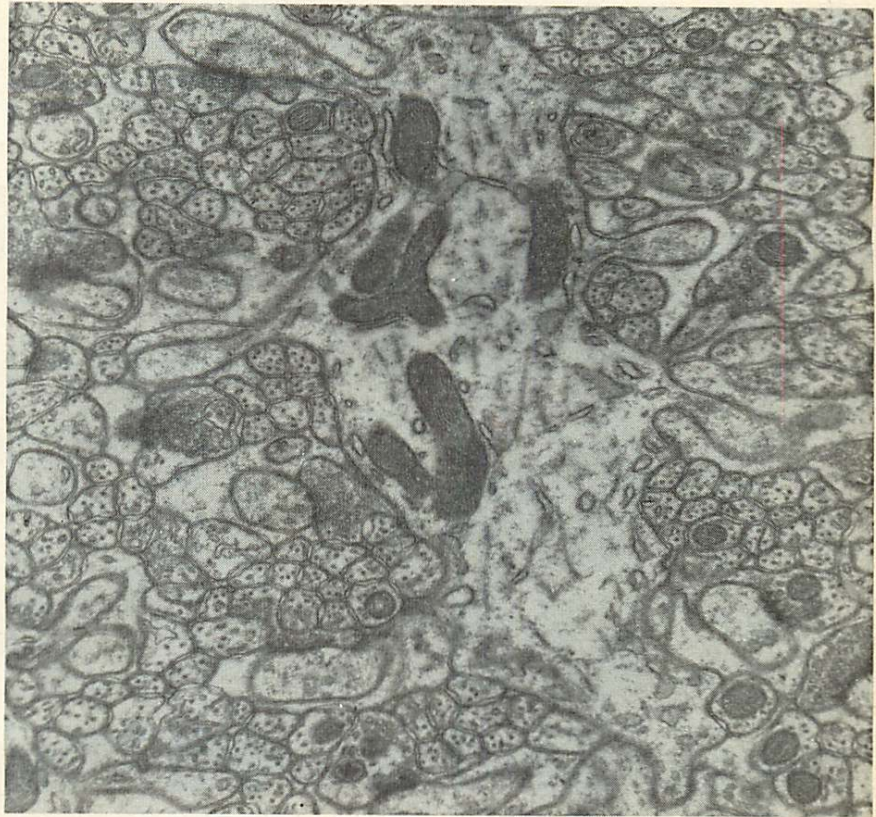
Organization of the Neurons

As we have seen, the activation of the cerebellar cortex through the climbing-fiber system is relatively straightforward: the stimulation of a single climbing fiber elicits a powerful response from a single Purkinje cell. The sequence of events that follows on the stimulation of a mossy fiber is not only more complicated but also inherently less predictable.

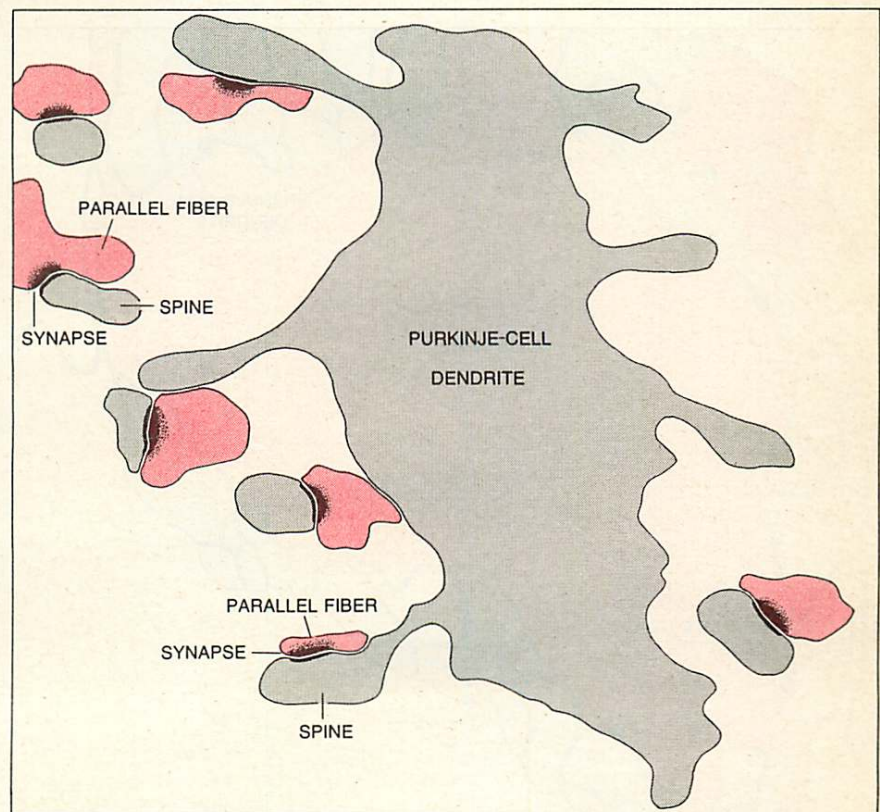
The initial sequence of events was first suggested by János Szentágothai of the Semmelweis University School of Medicine in Budapest: the stimulation of a small bunch of mossy fibers activates, through the granule cells and their parallel fibers, an extensive array of Purkinje cells and all three types of inhibitory interneuron. Subsequent interactions of the neurons tend to limit the extent and duration of the response. The activation of Purkinje cells through the parallel fibers is soon inhibited by the basket cells and the stellate cells, which are activated by the same parallel fibers. Because the axons of the basket and stellate cells run at right angles to the parallel fibers, the inhibition is not confined to the activated Purkinje cells; those on each side of the beam or column of stimulated Purkinje cells are also subject to strong inhibition. The effect of the inhibitory neurons is therefore to sharpen the boundary and increase the contrast between those cells that have been activated and those that have not.

At the same time the parallel fibers and the mossy fibers have activated the Golgi cells at the granule-cell level. The Golgi cells exert their inhibitory effect on the granule cells and thereby quench any further activity in the parallel fibers. This mechanism is one of negative feedback: through the Golgi cell the parallel fiber extinguishes its own stimulus. The net result of these interactions is the brief firing of a relatively large but sharply defined population of Purkinje cells.

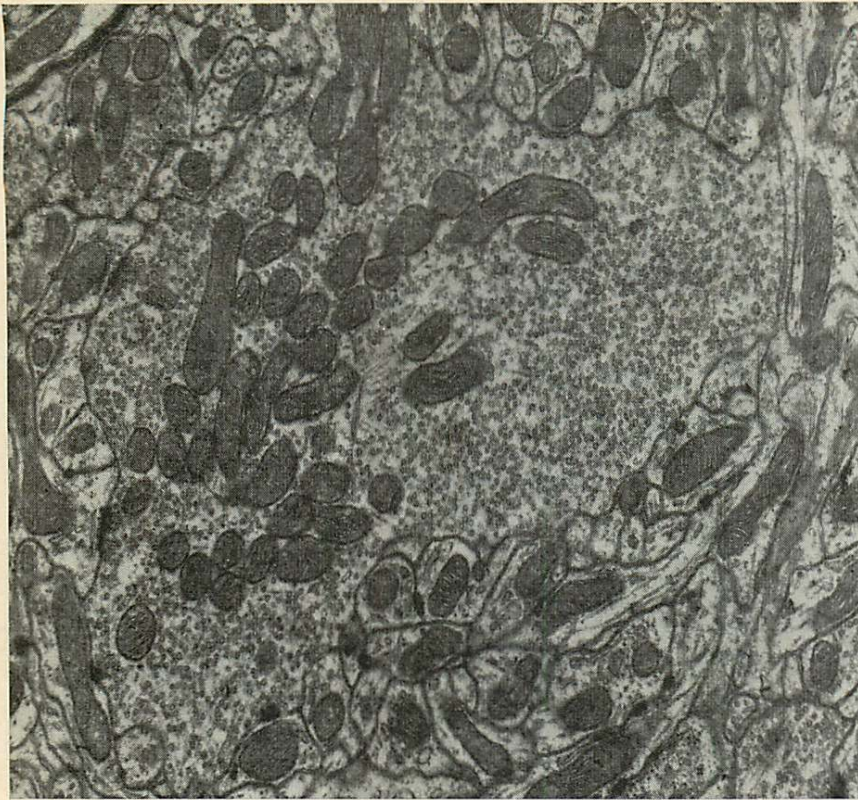
At about the time the functional properties of these neuronal circuits were being elucidated an observation made by Masao Ito and his colleagues at the University of Tokyo changed our perspective on the behavior of the entire system. Ito and his co-workers discovered that the Purkinje cell is itself an inhibitory neuron. The entire output of the elabo-



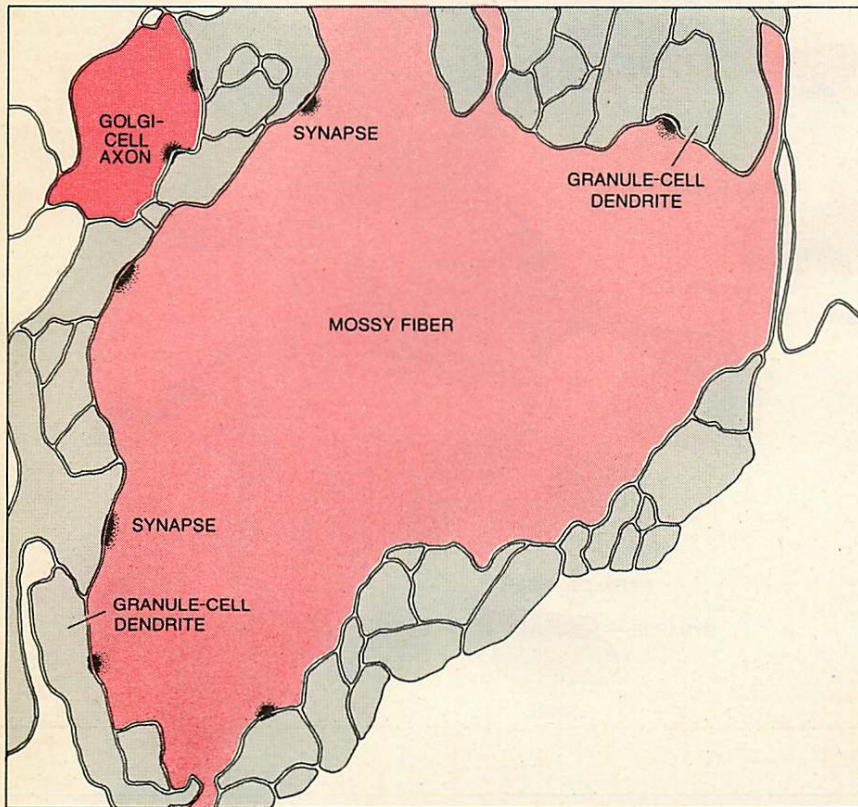
PARALLEL FIBERS attach to a Purkinje-cell dendrite in an electron micrograph made by Hillman. The dendrite is sectioned longitudinally; the parallel fibers are cut transversely.



SYNAPSES between parallel fibers and the Purkinje-cell dendrite are indicated in a diagram identifying the elements of the electron micrograph at the top of the page. The region of the dendrite shown is called a spiny branchlet; the spines form junctions with the parallel fibers. Each parallel fiber ordinarily makes only one contact with a given Purkinje cell.



CEREBELLAR GLOMERULUS is seen in cross section in another electron micrograph made by Hillman. The cells of the mammalian tissue are identified in the diagram below.



MOSSY FIBER forms synapses with the terminal dendrites of many granule cells in the cerebellar glomerulus. In addition the axons of Golgi cells make contact with the same granule-cell dendrites. The glomerulus forms on an enlarged segment of the mossy fiber.

rate neuronal network in the cerebellar cortex is therefore the organized, large-scale inhibition of other neurons in the cerebellar nuclei. Furthermore, it became evident that of the cells residing in the cortex only the granule cells are excitatory; all the rest are inhibitory. This work provided a fundamental insight into the functioning of the cortex. The firing of the nerve cells that give rise to the climbing fibers and the mossy fibers produces rapid activation of the cerebellar nuclei and through them of cerebral and spinal systems. This activity is abruptly terminated by the inhibitory signals from the cortex.

In several ways the model of the cerebellar cortex devised in these early studies was too simplistic. Although it described with some accuracy the neuronal response to an abrupt stimulus, such as an externally applied electrical potential, it was inadequate to describe the activity following the physiological stimuli constantly impinging on the cortex under ordinary circumstances. For example, the inhibitory interneurons of the molecular layer probably do not normally obliterate the activity of entire groups of Purkinje cells while allowing others to fire. It is more likely that they serve to set a threshold of excitability and thereby to regulate the dynamic range of activity in the cortex. The Golgi cell, on the other hand, is probably a central element in cerebellar organization. Through its direct contacts with the climbing fibers and the mossy fibers the Golgi cell probably "selects" what inputs reach the Purkinje-cell layer at a given time.

In spite of its limitations our study provided a foundation for constructing a theory of cerebellar function. The description of the interactions between the neuronal elements of the cortex was comprehensive and detailed, even if it was based on observations made under somewhat artificial circumstances. Furthermore, the study represented the first demonstration of a correlation between structure and function in a major lobe of the brain.

The Function of the Cerebellar Cortex

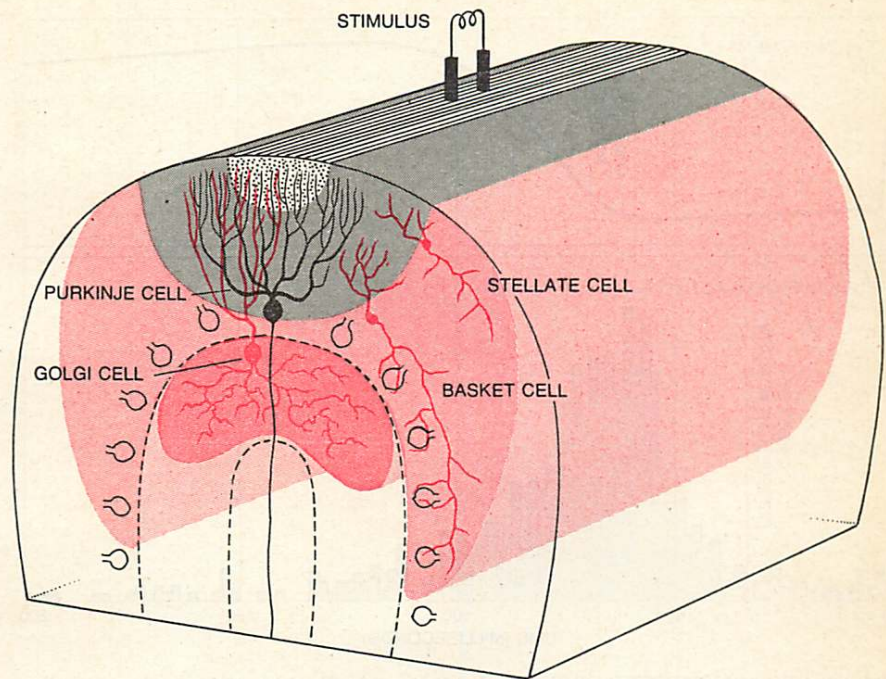
If we are finally to understand the significance of the neuronal circuits in the cerebellar cortex, we must analyze those circuits in terms of the kind of information they ordinarily receive. The techniques available for this task are necessarily less direct and less precise than dissection and staining or probing with an electrode, but they have nevertheless yielded important results. One of

the most profitable techniques has been the mapping of projections onto the cerebellum. This consists in selecting a nerve fiber of known origin or destination outside the cerebellum and determining the point at which it impinges on the cerebellar cortex.

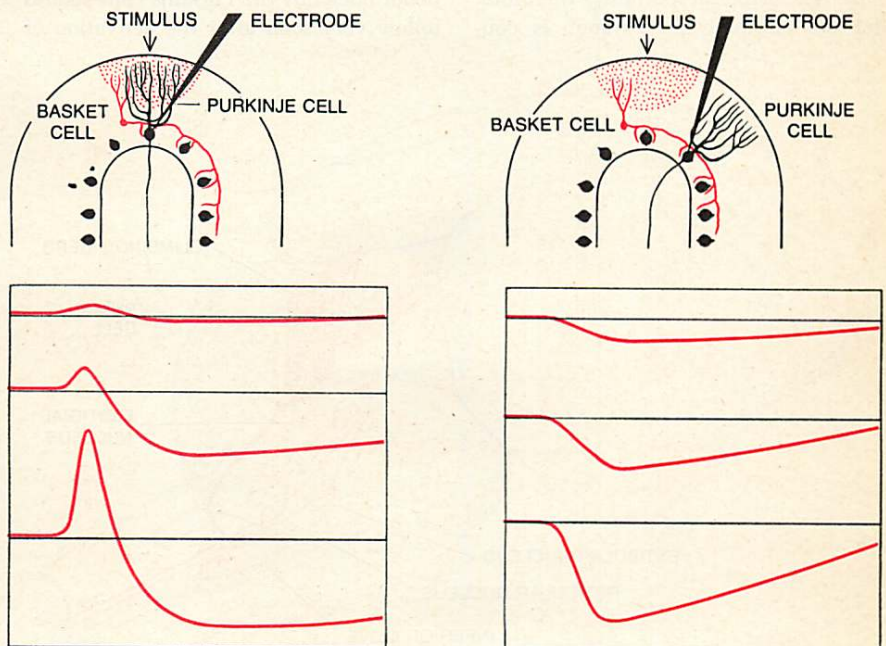
Each of the proprioceptive nerve endings in the skeletal muscles, for example, corresponds to a particular position on the surface of the cerebellum. When the sum of these positions is plotted, the result is a map such as the one that has been compiled over a period of many years by Olov Oscarsson of the University of Lund and by D. Armstrong and R. J. Harvey of the University of Bristol. By recording the projections of the climbing fibers they have discovered that these afferent cells are distributed with remarkable orderliness in the cerebellar cortex: they are organized in strips parallel to the median line and covering large areas distributed over many folds in the cortex [see bottom illustration on next page].

These maps confirm the earlier findings of Jan Voogd of the University of Leiden, who studied the effects of small lesions in the inferior olive, one of the principal sources of the climbing fibers. Nerve fibers radiating from a lesion usually degenerate, and Voogd found in this case that patterns of degenerating tissue on the cerebellar cortex assumed the form of long strips oriented from the front of the head to the back, that is, parallel to the median plane. His discovery suggests that the longitudinal strip is an important principle of organization in the projection of the climbing fibers onto the cerebellar cortex. The pattern has been detected in several vertebrate species.

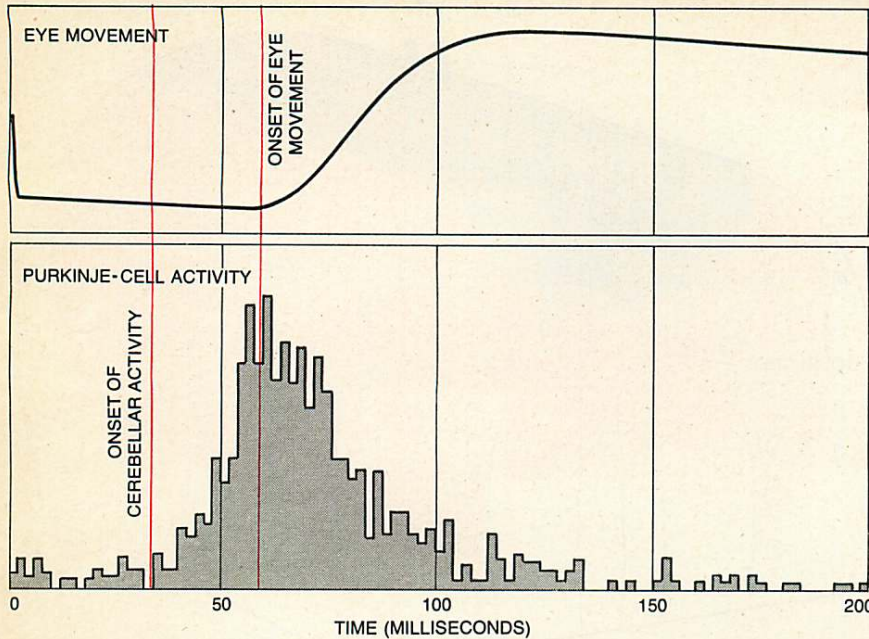
A clue to the significance of this organizational pattern has recently been provided by pharmacological studies of the cortex. The experiments were performed by Y. Lamarre and C. de Montigny of the University of Montreal and by R. A. Volkind and me at the University of Iowa. They involved a drug called harmaline, derived from the herb harmal, which causes tremors; we have shown in the cat that the effects of the drug are traceable to the activation of the inferior olive. An immediate and obvious inference is that the inferior olive, with the fibers it projects to the cerebellar nuclei and the Purkinje cells, is part of a motor command system concerned with muscular movement. There is even a reasonable basis for speculation on what kind of movements are involved. When maps derived from the proprio-



SPATIAL DISTRIBUTION of excitation in the cortex is determined largely by inhibitory neurons. When a brief electrical stimulus is applied to the surface of the cortex, a small bundle of parallel fibers (*stippled area*) is activated and excites the dendrites of all the fibers immediately under it (*gray*). The stimulated fibers excite Purkinje cells, stellate cells, basket cells and Golgi cells. The firing of the Purkinje cells constitutes the sole output of the cortex; the other neurons serve to define which Purkinje cells can fire. Because the axons of basket cells and stellate cells extend at right angles to the parallel fibers in the molecular layer, they inhibit Purkinje cells in a wide area on both sides of the excited region (*light color*). The Golgi cells generate an area of inhibition in the granule cells directly under the activated array of parallel fibers (*dark color*). Because the parallel fibers are the axons of the granule cells, inhibition by Golgi cells tends to terminate the excitation.



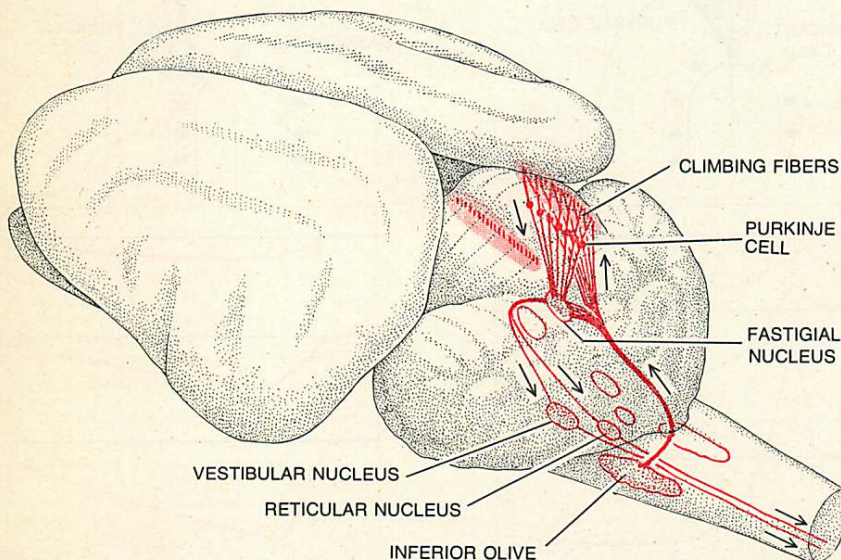
STIMULATION AND INHIBITION of Purkinje cells follow an established temporal sequence. When the response of a cell directly under the stimulated area is recorded (*left*), a brief period of activation is observed (*upward deflection*), followed by a longer period of inhibition (*downward deflection*). The activation results from the direct stimulation of the Purkinje cell by parallel fibers, the inhibition from the action of basket cells and stellate cells. The magnitude of the response varies with the intensity of the stimulation. When the response of a laterally located Purkinje cell is monitored (*right*), only the inhibition is observed, since only basket-cell axons, not stimulated parallel fibers, reach Purkinje cells.



RAPID EYE MOVEMENTS called saccades are associated with activity in the cerebellar cortex. The top graph is an averaged record of 100 saccades; the bottom graph records the activity of a single Purkinje cell during the same 100 eye movements. Purkinje-cell activity begins to increase about 25 milliseconds before the movement is initiated, which suggests that the cerebellum can coordinate or correct such movements before they are generated.

ceptive sensors are superposed on the longitudinal strips that are associated with the climbing fibers, it is found that the climbing-fiber patterns overlap the projections of several areas of the body. It is the current hypothesis, therefore, that the climbing-fiber system is con-

cerned with synchronous movements of groups of muscles, probably involving more than one limb. There is also reason to believe it mainly influences rapid movements. The inhibition of the cerebellar nuclei by the Purkinje cells should follow very soon after the activation of



PROJECTION OF CLIMBING FIBERS onto the cerebellar cortex reveals an orderly distribution. The fibers originate in the two inferior olives of the brain stem. Fibers from each olive terminate in the opposite hemisphere of the cerebellum. There they are organized in longitudinal strips covering many cortical folds. The length and orientation of these strips suggest that the climbing-fiber system participates in the regulation of movements that involve several limbs, since each strip extends across areas known to be associated with several parts of the body. Branches of the climbing fibers also reach the cerebellar nuclei (the fastigial nucleus is shown here) and are joined there by the axons of Purkinje cells from the cortex. The output of the fastigial nucleus is applied to the vestibular and reticular nuclei.

the nuclei, generating a powerful but brief command signal.

A comprehensive analysis of the mossy-fiber system is more difficult to achieve. The effects of mossy-fiber stimulation are so different from those of the climbing fibers that it is possible the two systems are "time-sharing" the Purkinje cells, each employing them for quite different purposes. Not only do the mossy fibers activate large areas of the cortex instead of individual cells; they also enlist the aid of the inhibitory interneurons, which may modulate and detect patterns in incoming signals. The Golgi cells in particular may be involved in determining what kinds of information reach the cortex through the parallel fibers; moreover, in any time-sharing arrangement they could apportion the Purkinje cells between the two systems.

An example of a motor behavior that is linked with the mossy-fiber system has recently been encountered in studies of visual coordination. In organizing the delicate and precise movements of the eyes the cerebellum is evidently essential; cerebellar dysfunction often disrupts such movements. Two regions of the cerebellum are known to participate in these functions. One is the floccular-nodular area; it regulates the position of the eyes with respect to the orientation of the head and body, enabling one to stare at a fixed point while moving. The other is the cerebellar vermis, which is believed to control the rapid eye movements called saccades, which are important in visual tracking.

In a recent series of experiments at the Air Force School of Aerospace Medicine, James W. Wolfe and I showed that the activation of Purkinje cells by mossy fibers increases about 25 milliseconds before an eye movement begins [see top illustration at left]. The implication of this discovery is that cerebellar regulation of movement through the mossy-fiber system is capable of correcting mistakes before they have reached the muscles and have been expressed in actual movement. The cerebellum appears to correct these movements by acting as a brake.

Motor Coordination

There is no longer any doubt that the cerebellum is a central control point for the organization of movement. It does not initiate movement, and indeed movement can be generated in the absence of a cerebellum. It modulates or reorganizes motor commands, and by coordinating diverse signals it obtains the maximum efficiency from them. It is there-

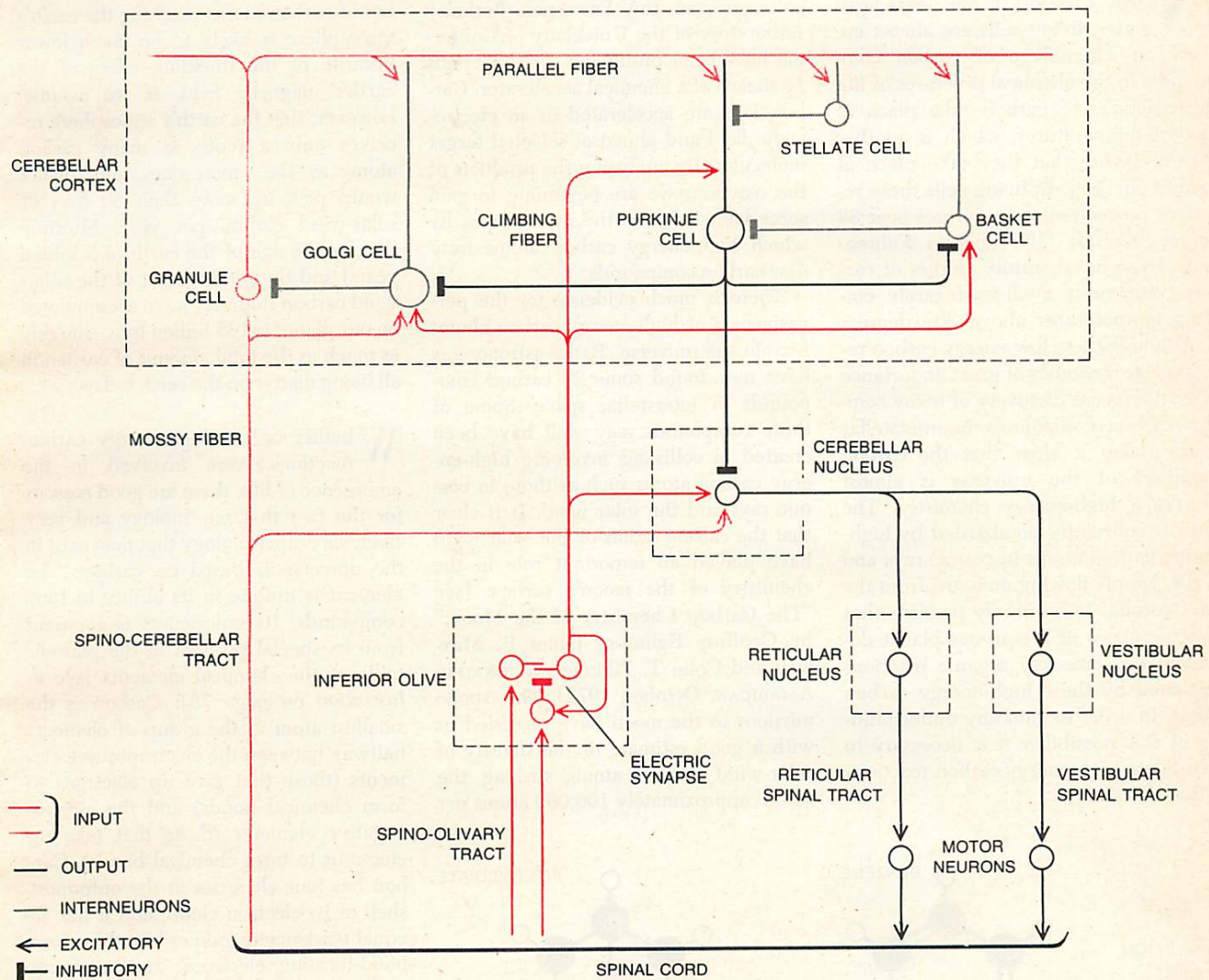
fore an organ of regulation in the highest sense. It may in fact regulate more than motor performance. R. Nieuwenhuys and C. Nicholson of the Catholic University of Nijmegen have shown that in electric fish (family Mormyridae) employing an electric field as a sensory organ the cerebellum attains enormous size and fills most of the cranial cavity.

Without question the cerebellum is far more sophisticated than the simple control box, comparing muscle position with brain command, that Sherrington and his contemporaries supposed it to be. Israel Gelfand, M. L. Shik and their associates at the Institute of Information Transmission Systems in Moscow have shown that the cerebellum is capable of coordinating movement even in the

absence of all information from the periphery of the body. They removed the forebrain and blocked proprioceptive sensation in experimental animals; as long as the cerebellum remained intact locomotion was possible, but it was disrupted when the cerebellum was removed. A series of experiments conducted by Anders Lundberg and his colleagues at the University of Göteborg provides a further indication that some cerebellar activity is concerned with the internal state of the central nervous system. They found that one of the main afferent tracts leading to the cerebellum, the ventral spinocerebellar tract, conveys information not about the state of the body or the external environment but about the activity of inhibitory in-

terneurons in the spinal cord. Such an internal monitoring mechanism might be a necessity in a system intended to refine or revise motor commands before they reach the muscles, such as is observed in the cerebellar control of eye movement.

Excellence in motor coordination is obviously an adaptive advantage, and evidently it is enough of an advantage to sustain the development of a specialized brain center committed primarily to that purpose. The success of the motor coordination center is suggested by the calculations of Sherwood L. Washburn and R. S. Harding of the University of California at Berkeley. They report that the cerebellum has enlarged between threefold and fourfold in the past million years of human evolution.



SCHEMATIC "WIRING DIAGRAM" of the cerebellar cortex and the brain centers with which it communicates relates the structure of the nerve-cell circuits to their function. The types of cells and synapses are identified in the key at lower left. Input to the cortex is through the climbing fibers and mossy fibers, both of which also send branches to the cerebellar nuclei. In the cortex both fibers ultimately act on the Purkinje cells; in addition the response of

these cells is influenced by three kinds of interneurons, all of them inhibitory. Since the Purkinje cell is also inhibitory its effect on the cerebellar nuclei is to prevent the transmission of nerve impulses from the climbing fibers and mossy fibers that would otherwise reach the motor neurons and generate movement. Thus the cortex appears to be an organ of regulation, empowered to select certain motor commands for transmittal and to veto all others.