'Silent' Cells: Quiet Revolution in Brain Science

Rat-tat-tat crackels the loudspeaker that reports firing of nerve cells as physiologists' fine electrodes penetrate the layers of a brain. During the last two weeks neuroscientists have examined evidence that a "silent revolution" is altering basic precepts of their field. Much, if not most, of the important information processing in the nervous system may involve cells that never fire and computations that never add up to a click.

More than a hundred scientists gathered in Boulder, Colo., for an intensive series of lectures and discussions organized by the Neurosciences Research Program, a research center of the Massachusetts Institute of Technology. In evaluating the "silent" aspects of brain function, the investigators examined topics ranging from proteins of red blood cells to the visual system of the fly. Local, rather than silent, was the adjective generally used to describe the interactions under consideration. One scientist suggested that attention was now focusing on signals comparable to small town radio broadcasts, while previous work had concentrated on nationwide news flashes.

The shift in emphasis results from new microscopic, electrophysiological and computer techniques. Scientists have become aware of how many small cells in the brain communicate only with their immediate neighbors. Furthermore the results of reconstructing the shape and all the interactions of a single cell from electron microscope images of hundreds of thin slices, along with sensitive recording of the electrical activity in specific cells, have revealed that nerve cells can communicate in an extensive variety of manners.

When pioneering neuroanatomist Ramon y Cajal in 1899 argued that individual nerve cells, rather than a continuous network, were the basis of the nervous system, he also established the concept of nerve-cell polarity. Generations of students have been taught that information enters a nerve cell via the dendrites, often a bushy tangle of threadlike processes, and spreads as an electrical current to the cell body. According to this model, a special area at the base of the cell body then adds up the input from all the dendrites and, if the sum is sufficient, initiates an all-or-none electrical spike that travels along another threadlike process, the axon. At junctions along the axon, the signal passes to the dendrites of other nerve cells.

Accumulating evidence indicates that at least some nerve cells communicate in more unorthodox ways. There are now examples of junctions that can pass information from other nerve cells directly into an axon and junctions that can transmit signals from cell dendrites. Even ability to generate long-distance spikes, the action potentials, is no longer confined to axons. Gordon M. Shepherd of Yale University listed dendrites that transmit action potentials and axons that do not. "There is no fixed relation between the kind of process [axon or dendrites] and the kind of activity," Shepherd says. "Neurons in different parts of the nervous system have different combinations of morphology and physiological properties."

Using electron microscopy, anatomists now observe synapses between dendrites, between axons, between cell bodies, and even occasionally from a dendrite to an axon. Sometimes they see several synapses in a small area and "reciprocal synapses" where information passes in opposite directions in a pair of side-by-side junctions. The retina (see micrograph) and the olfactory bulb were examined as parts of the nervous system where a complex pattern of synapses connect neighboring cells. French physiologist Henri Korn described paired junctions where information was transmitted by electrical and chemical means and activity of one part could control the activity of the other. Neuroanatomist Sanford Palay rejoiced, "We've had 15 years of trying to bring mixed synapses to the attention of

A theory of the brain: Edelman's quest for unity

Gerald M. Edelman

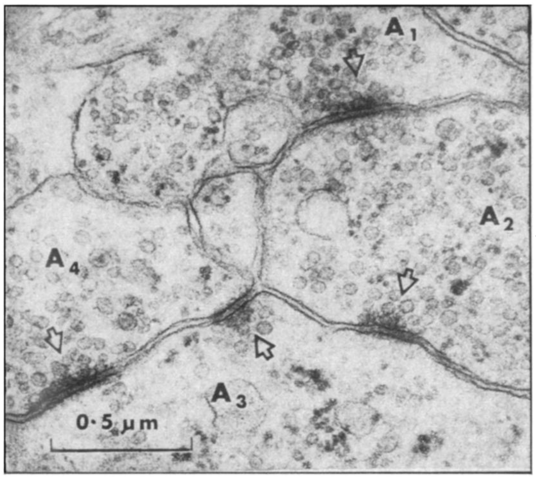
Fascinating, but disreputable, is the way Gerald M. Edelman describes the challenge of creating a unified theory of the brain on the basis of molecules, cells and their interactions. Yet as the climax, or at least an addendum, to two weeks of intensive lectures and discussions by a handpicked collection of leading neuroscientists and younger postdoctoral fellows (see above story), the Nobel Prize-winning immunologist from Rockefeller University offered an explanation of brain function. Edelman led into his 90-minute presentation with the comment that he is not as qualified as some others to consider the topic. But, he claimed, those neuroscientists he has tried to entice into speculation counter either that the field is not yet ready or that they will never announce their private theories in public. "Although our knowledge of subsystems, structures and functions is not ripe," Edelman insisted, "it may be fruitful to ask whether the higher brain operates according to a single principle." And he went on to suggest and defend such a principle.

Edelman's model stems from similarities between the nervous and the immune systems. Both can recognize a specific signal (in one case a message from the sense organs, in the other a molecule foreign to the body) and can store that recognition in a type of memory. Although the actual components of the systems are clearly different, Edelman suggests that principles of immununology may have been applied more generally during evolution. Evolution itself, for that matter, relies on the principle that Edelman sees underlying brain function. That basic process he calls selection. Just as natural selection permits an animal with particular, but preexisting characteristics to prosper at the expense of others and, as in immunology, a foreign substance stimulates reproduction of the cell bearing an antibody to that substance, so Edelman proposes that a complex signal from the sense organs selects among groups of nerve cells already wired together in the brain. Although the cells that respond may be altered by exposure to the signal, the signal does not actually create the connections between brain cells as some earlier theories about the brain have proposed.

"Are you there? Can I meet you? Are you able to act?" Edelman imagines a signal polling a large number of groups, each made up of 50 to 10,000 nerve cells. These groups comprise what Edelman calls the primary brain repertoire. He hypothesizes that a number of cell groups will match, or recognize, each signal and respond to some extent. Edelman calls this characteristic "degeneracy" in analogy to degenerate equations in physics that have more than one solution.

Once a match is achieved, it wouldn't do to let the whole thing decay away, Edelman says. Therefore, one exposure to a signal changes the likelihood that the group will respond the next time it is polled by that signal. Experimental evidence suggests, but does not yet prove, that such a long-lasting change results from alterations of the synapse structures, which pass information from one nerve cell to another.

Not only does a signal activate a number of cell groups in the primary repertoire,



John E. Dowling, *Proc. Roy. Soc. B*

Cluster of synapses links retinal cells.

physiologists."

Neuroscientists are considering not only new paths of signal transmission but also a wider range of chemicals to carry the signals between cells. Evidence is mounting that in addition to recognized transmitters, such as acetylcholine, some amino acids serve in the brain as transmitters. Researchers are studying other chemicals for more general effects on nerve cell activity.

The multitude of possibilities for cell communication has serious implications for ideas on how information is processed in the brain. The model cannot limit dendrites to being simply conduits for signals. In some cases the dendrite and axon may each weigh their own inputs and produce outputs independently of the cell body computations. "The neuron was considered a standard computer unit, but now we feel that it is too variable," explains Henry J. Ralston III of the University of California at San Francisco. "The functional organization of local regions is in terms of synaptic circuits, not local neurons."

A query important to the new ideas is how far within the nerve cell local signals spread. Unless they are propagated as action potentials, these electrical signals will fade over a distance, dependent on the size and shape of the cell region, the geometry of its branches and the characteristics of its membrane. Researchers who make mathematical models of nerve cells to evaluate signal spread disagree on just how local is local—whether the cell body hears all or nothing of the activity in its branches. Wilfrid Rall of the National Institute of Arthritis, Metabolism and Digestive Diseases made a plea to the physiologists. He asked that when the experimenters sink electrodes into cells, they measure the parameters needed by the researchers who make theoretical models. To settle how much a cell body learns of the chatter in its distant branches, the theoreticians need measured electrical properties of cells whose detailed structure is also known.

Although the researchers generally agreed on the importance of being alert to the local, silent interactions, which would be missed by electrodes eavesdropping outside nerve cell boundaries, the details of those interactions are far from settled. Itzchak Parnass of Hebrew University in Jerusalem summarizes: "Each of us has an answer taken from one experimental system. Each rule right for one system is not right for another." Rodolfo R. Llinas of New York University Medical Center agrees. "It's time to be looking at different synapses, rather than generalizing." □

according to Edelman's model, but those groups activate other cell groups in a secondary repertoire, groups which Edelman calls R of R (recognizers of recognizers). An R of R group can respond, in addition, to the output of other R of R groups.

Consciousness, according to Edelman, is the result of cyclic repetition of sequences of events. "I see the brain as a seething mass of patterns going on and off all over the place," he says. In the first phase of cycling, signals are recognized by a cell group of the primary repertoire, and that group's output is recognized by several R of R groups, which fire repeatedly in their typical patterns. In a latter cycle, those processed signals can re-enter the arena and poll further R of R groups simultaneously with newly processed signals. "Such a system is designed so that an internally generated signal is re-entered *as if it were an external signal,*" Edelman says. This feature, he explains, provides a means of dealing with novelty and for reviewing internal states, in the context of new sensory inputs.

Edelman argues that his model could allow a brain to deal with new information, such as a new symphony, which neither it nor any other brain during evolution had previously confronted. He also believes that his model is sufficient for explaining consciousness and self-awareness. In addition, the room for individuality in how the cells respond implies a considerable degree of freedom and free will. "And it involves no little man who does the thinking," Edelman concludes, "and no infinite regress, such as 'who is guarding the guardian?' "

The listening neuroscientists, who had been provided before with an 80-page description of Edelman's model, questioned him during the next hour as if they were holding a giant oral thesis examination. First several respected elders made prepared comments to which Edelman replied, and eventually a few of the young conference participants asked questions. Edelman occasionally looked for support to senior neuroanatomist Vernon Mountcastle, who was chairing the meeting, for specifics on the arrangements of brain cells.

Speaking early because he had to catch a bus to catch a plane to return to Hungary, anatomist John Szentagothai gave general approval to the theory, saying that it fit the current knowledge of brain cells and their connections. He suggested, however, that re-entry of processed signals would allow too many possibilities. "Inhibition would have to be extremely sophisticated. How can it all be kept in check?" he asked. Szentagothai also questioned, on the basis of his experience in neuroscience since the 1930s, whether the area had matured to a stage where there were enough established facts for researchers to usefully begin such an extensive theoretical enterprise.

Other respondents were concerned about the actual composition of the basic group of cells, especially how an experimenter would recognize such a group. They also discussed at what point in evolution of the complex brain there would be enough cells and flexibility for a selective, degenerate mechanism, such as Edelman was suggesting. The greatest underlying concern, however, was whether Edelman's model was so general that it could not be tested by specific experiments. "This model will be difficult to disprove," Edelman admitted.

Comments by the younger scientists during informal discussion that continued over coffee on the conference buses and during cocktails revealed interest in Edelman's synthesis of ideas, but some skepticism over his model's usefulness. One young neurophysiologist advised, "Don't title your story 'Brain Solved' until we get some experimental evidence."

Thermonuclear burn in laser fusion

Imploded-pellet fusion is the name usually given to a whole class of experiments that are attempting to achieve controlled thermonuclear fusion by exciting mini explosions in tiny pellets of fuel. The explosions are expected to result from implosions of the fuel pellets caused by bombardment by laser light, beams of accelerated electrons or beams of accelerated ions. Such crushing of the fuel pellets, it is hoped, will induce in the center of the fuel mass the temperatures and densities characteristic of "thermonuclear burn," the state found in H-bombs and desired in any controlled fusion system.

Recent years have recorded the generation of nuclear fusions in pellet targets crushed by laser light and by electron beams. But fusions can be generated in the crushing of the pellet without necessarily achieving nuclear burn conditions in the material in the core of the pellet. Now, from the Lawrence Livermore Laboratory, one of the four major centers of laser-fusion research in the United States, comes a report claiming achievement of thermonuclear-burn conditions in the center of a laser-imploded pellet, one of the criteria necessary for practical use of the method. Until this report, by N. M. Ceglio and L. W.