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Overturning Theories in Neurobiology

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Department Editor

Although we really know very little about the living world, our ignorance is nowhere more profound than when it comes to the nervous system. How is visual perception created? What is a memory? How do brain cells come to organize themselves correctly during development? We cannot answer any of these questions adequately, and since our knowledge of the nervous system is so inadequate, the theories we develop are very tentative. The fact that theories in this field are constantly being toppled as new evidence becomes available is a good indication of the depths of our ignorance. But this situation is exciting rather than depressing. The nervous system is full of surprises to excite us and our students. For this column I've selected a few items that I find particularly intriguing.

Weeding Out Neurons

How does a brain with billions of neurons organize itself? A single neuron may make a thousand connections with other cells. How is it guided in making these connections, and what happens if it makes a mistake? It has become more and more obvious with observation that a weeding-out process occurs during development; that is, neuron cell death and synaptic degeneration are necessary for the normal development of the nervous system. This observation originally was made almost 80 years ago, so it's hardly new, but the progressive developmental events during neurogenesis are so striking and obvious that this other side of development, these 'regressive events' have been virtually ignored (Cowan, Fawcett, O'Leary & Stanfield 1984).

The extent of cell death during neurogenesis is significant in many parts of the nervous system. In the chick, 75 percent of the cells die in the trigeminal nerve's mesencephalic nucleus, and in the majority of brain structures about half the neurons that form initially die during development. Why is this cell death necessary? One function is to match the size of a neuron group to the size of its target field. Another is to eliminate neurons that have made erroneous connections. The mechanisms leading to the preferential death of certain neurons are unknown, but competition for trophic factors such as nerve growth factor may be involved.

Most neuronal cell death occurs relatively early in development. This is followed by a second weeding-out mechanism, the elimination of axonal processes and synapses. For example, at birth five or six axons form synapses with each muscle fiber, but in mature animals most muscle cells are innervated by only one axon. In the brain a similar situation is seen in the connections between cerebellar Purkinje cells and climbing fibers. In both cases, the most active synapses appear to be the ones that survive (Cowan 1979).

The role of activity in synapse formation has been studied from a different viewpoint by tricking a system into recapitulating the process. A muscle nerve is transplanted into a nonsynaptic region of another muscle whose own nerve has been severed (Lømo 1983). New synapses begin to form within a few days. The first step is the appearance of acetylcholine (ACh) receptors on the denervated muscle fiber. These quickly cluster under foreign nerve terminals as these sprout, possibly because of release of growth factors from the muscle membrane. Only hours after the ACh receptors cluster, synaptic transmission is effective enough to evoke muscle contraction. Further maturation, including the appearance of acetylcholinesterase, requires impulse activity. Thus it appears that both trophic factors and activity are needed for synaptogenesis.

Regeneration and Transplantation

This work on the regeneration of nerve endings indicates that the mature nervous system retains some plasticity, particularly in the ability of synapses to modify their activity, be replaced, or change in number. Writing on synaptic plasticity, Cotman and Nietro-Sampedro (1984) describe the synaptic alterations caused by brain lesions. New synapses can grow in the mature central nervous system (CNS), but axonal regrowth occurs only over very short distances. The regrowth takes several weeks, and its rate depends upon the rate at which degenerating synapses are cleared away. It appears that injured tissue releases specific trophic factors which speed growth. This observation has important consequences for transplantation of brain cells. It has been discovered that transplants survive better in injured than in uninjured tissue. The trophic factors released by the damaged tissue seem to enhance cell survival, so in the future small brain lesions may be produced several days before transplantation to ensure growth of the grafted tissue. Of course, as Cotman and Nietro-Sampedro point out, "Transplants into the mature CNS do not fully reform the native circuitry and seem to act primarily by delivering chemicals to the proper area much as an endogenous drug delivery system."

While whole brain transplants belong in the realm of science fiction, the grafting of small pieces of tissue into the brain is definitely within the realm of possibility. In fact, it has been tried on a small number of humans suffering from Parkinson's disease, a deterioration of a part of the brain that releases dopamine, a neurotransmitter also produced by the adrenal cortex. When tissue from the patient's own adrenal glands are grafted into the brain, the disease

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symptoms have in some cases subsided, though not disappeared (Kolata 1983a).

While this work seems promising, Parkinson's disease is a special case, since the patient's own tissue can be used in the graft. In other cases fetal brain tissue, grown in culture, would be necessary because adult tissue isn't plastic enough to form sufficient connections. Rejection isn't a problem in brain grafting because the blood-brain barrier prevents immune cells from entering brain tissue. Researchers have produced brain damage in rats similar to that found in human patients with Alzheimer's disease in which ACh-releasing cells deteriorate and memory fails. These animals' memories improve when they receive grafts of fetal tissue that makes ACh, but similar operations in humans must await the results of further animal research.

New Neurons

While new synapses develop in the mature brain, it has been accepted for some time that new neurons do not. Like numerous assumptions about the nervous system, this one is being overturned, toppled by an intriguing series of experiments. Canaries sing, but only male canaries. Fernando Nottebaum has discovered the parts of the brain that respond to sound (the nucleus hyperstriatum ventralis, par caudalis, or HVc) and activate voice (the robust nucleus of the archistriatum). In the spring under natural conditions, these areas grow under the influence of testosterone and shrink in the fall as the hormone levels wane. This size change is not due merely to a change in connections between neurons, but to a change in neuron number. Male canaries have about 41,000 HVc neurons in the spring, but only 25,000 in the fall. The number increases again the next spring because of another spurt of hormone-induced neuron growth (Kolata 1984a). This change in neuron number affects brain function; male canaries do not sing in the fall because the destruction of neurons seems to cause destruction of memory. When the cell number increases again in the spring the birds learn new songs with which to attract mates. The most intriguing thing about Nottebaum's findings is that new neurons are also found in the cerebellum, midbrain, and medulla of canaries and of other bird species as well. So new neurons seem to be a rather common phenomenon, at least in birds. It's amazing that this was not discovered earlier, again indicating the rudimentary state of our knowledge of the brain. Because we know so little, surprises become almost commonplace.

Electrical Connections

Another standard piece of wisdom that has turned out to be less than certain is that the neurons in higher animals communicate almost exclusively through chemical synapses, and that electrical communication is found mostly in lower animals. Now such communication has been discovered in the mammalian hippocampus, hypothalamus, and olfactory cortex ("*Nature* Survey" 1981). But if chemical synapses allow for more flexibility and modulation, why are these supposedly more primitive electrical connections surprisingly common not only in the brain but the spinal column and retina? First, electrical synapses transmit signals more rapidly than do chemical synapses where the release of neurotransmitter and its attachment to postsynaptic receptors slows down the signal. In electrical synapses, the cells are physically linked by hexagonal structures composed of the protein connexin. Electrical junctions may also be useful in allowing two-way communication between neurons. Reciprocal signaling may be important when groups of neurons have to coordinate their activity.

One reason electrical synapses have been overlooked is that there is such exciting work going on with chemical synapses. The concept of the neurotransmitter is changing and the assumption that a neuron releases a single transmitter substance turns out to be far from true. The classical neurotransmitters which have been studied for many years are relatively small molecules. They include ACh, monoamines (norepinephrine, epinephrine, dopamine, serotonin, and 5-hydroxytryptamine - 5HT) and amino acids (glycine, glutamine, and α-aminobutyric acid). Many researchers are ready to add a new transmitter to this list. Adenosine, the ubiquitous purine found in nucleic acids, ATP, and cyclic AMP, may serve as a neurotransmitter ("*Nature* Survey" 1981). It may be released in inhibitory synapses in the brain and in some pathways of the autonomic nervous system. Solomon Snyder (1984) speculates that caffeine's ability to block adenosine receptors might be responsible for its behavioral effects.

While the search for small molecules that function as neurotransmitters is obviously still reaping results, it is in the field of neuropeptides that the search for new brain chemicals has proved most fruitful, perhaps too fruitful. These peptides are being discovered at such a rapid rate, that it will take some time to decipher the exact action and significance of each (Newmark 1983). These peptides were not discovered in the brain until recently because their concentrations are several orders of magnitude lower than those of the classical neurotransmitters. Many of the neuropeptides also have functions outside of the nervous system; many are associated with the gastrointestinal tract, including gastrin, somatostatin, cholecystokinin (CCK), insulin, and glucagon. Dorothy Krieger (1983) explains this commonality of brain-gut peptides as an indication of the development of these substances at a time early in evolution before separate nervous and endocrine systems had developed.

Neuropeptides have been discovered that relieve pain—enkephalins and dynorphin (Iverse 1982), control appetite—CCK (Kolata 1982), and affect memory—vasopressin (Krieger 1983), as well as performing a variety of other activities. But their mode of action has been difficult to decipher. Some researchers refer to neuropeptides as neuromodulators rather than neurotransmitters. While the latter produce rapid, short-term effects in a postsynaptic neuron, the former produce effects that have a slower onset and a longer duration. An observation that may clarify the role of neuropeptides is that a classical neurotransmitter and a neuropeptide are often found coexisting in the same neuron. This contradicts the commonly held assumption that, except during development, one neuron releases one neurotransmitter. In many areas of the brain this coexistence may be the rule rather than the exception (Hökfelt, Johansson & Goldstein 1984). The peptides support the action of classical transmitters. For example, the release of neuropeptide Y occurs preferentially at the higher firing frequencies of norepinephrine neurons. Rat medullary neurons that release 5HT also contain substance P and thyrotropin-releasing hormone (TRH). Both peptides enhance 5HT transmission: TRH by cooperating with 5HT at the postsynaptic receptor and substance P by blocking inhibitory presynaptic receptors.

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Still More News

I find the nervous system an especially exciting and engrossing topic to teach, and I've looked forward to writing this column for some time. But it has proved a more difficult task than I'd expected. The problem I encountered is similar to that faced by researchers in this rich and complex field: there is just too much going on! I came across so many fascinating topics that I could only discuss a small fraction of them, yet the rest are too interesting to omit. I'll quickly mention some, including references, so you can peruse them further if you find them as arresting as I did.

Memory is still an enigma. But Eric Kandel's work on conditioning and memory in the snail, *Aplysia californica*, indicates that significant progress can be made toward understanding memory by working with simple neural systems (Kandel 1979; Kandel & Schwartz 1982). For those interested in the molecular basis of memory, there is now evidence that a structural protein in neurons called fodrin may be responsible for changes in the postsynaptic neuron that correlate with long-term memory (Burns 1985).

As far as learning in humans is concerned, novel work is being done on learning in utero (Kolata 1984b). It involves pregnant women reading Dr. Seuss's *The Cat in the Hat*, and it seems to show that their newborn infants recognize this literary classic in tests done two days after birth! Another provocative line of research indicates that there is a relationship between left-handedness and both mathematical giftedness and immune disorders (Kolata 1983b). Excess testosterone during fetal life may alter brain anatomy so the right hemisphere, which is thought to be related to mathematical talent, becomes dominant. Norman Geschwind, who has developed this hypothesis, says that the association with the immune system arises because many of its genes are sex-linked.

When several young addicts developed symptoms similar to those of Parkinson's disease, two California neurologists went on the trail of the synthetic heroin these addicts had taken (Langston 1985). The drug contained MPTP, a toxin that binds to and destroys cells in the substantia nigra, the brain area affected in Parkinson's. This unfortunate occurrence has given researchers a new lead in the study of this disease. They are now looking for milder toxins that the general population might be exposed to, and that might lead to the slow deterioration of the substantia nigra seen in elderly patients with Parkinson's.

Though I must end here, I'll just mention that new work on the chemistry of dim-light receptors in the retina indicates that cyclic GMP and not calcium is responsible for the transduction of a light stimulus into an electrical signal (Lewin 1985; Altman 1985). So another theory is being overturned, again proving my point that the toppling of widely-accepted theories is the rule rather than the exception in nervous system research. This makes the teacher's knowledge rapidly obsolete in this area, but it also means that, while the study of the nervous system may be confusing, frustrating, and challenging, it is never boring!

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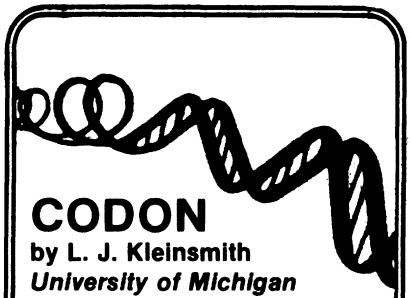

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