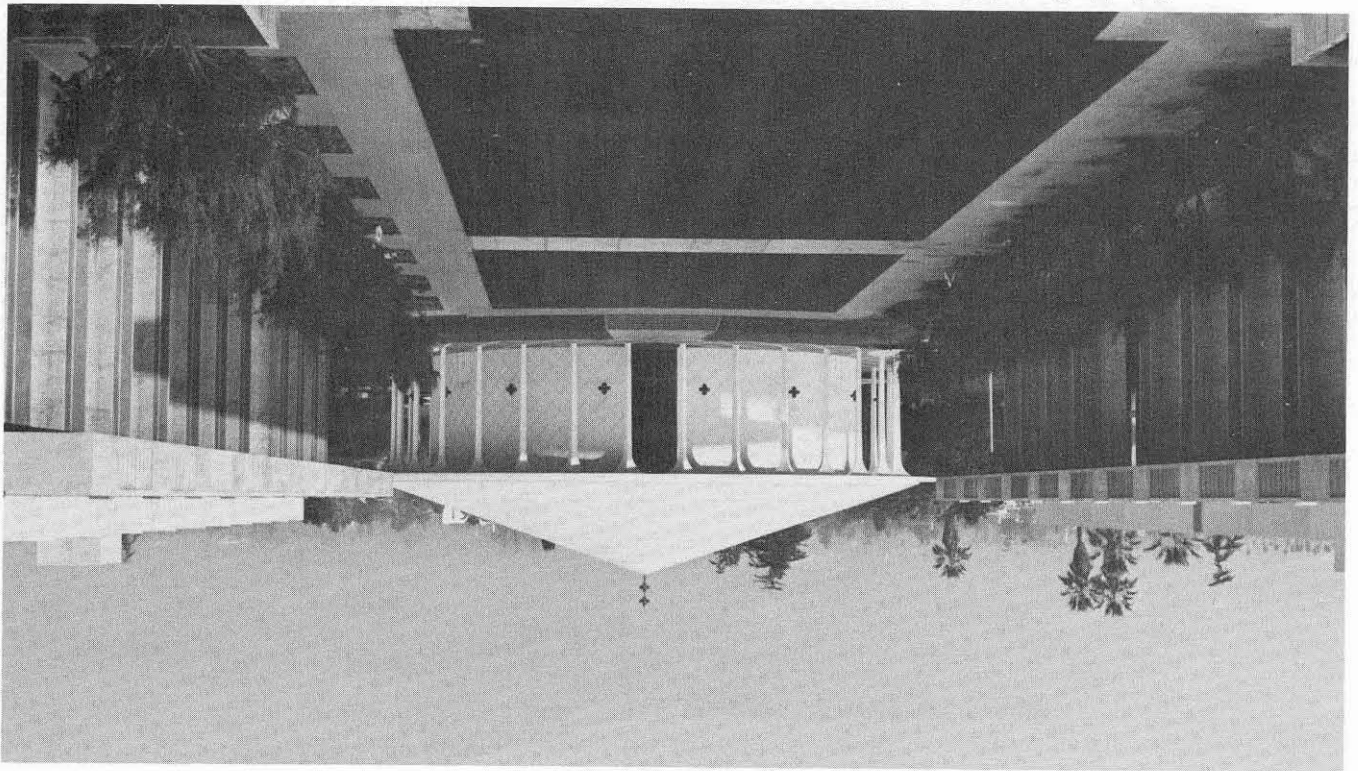


**Engineering  
and Science**

California Institute of Technology | January 1974

A SPECIAL  
ISSUE ON  
BEHAVIORAL  
BIOLOGY AT  
CALTECH

Caltech's Court of Man and the new Mabel and Arnold Beckman Laboratories of Behavioral Biology



# Engineering and Science

January 1974 / Volume XXXVII / Number 3

## A Special Issue on Behavioral Biology

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## In This Issue

Behavioral biology—the study of the biological basis of behavior—is a relatively new scientific discipline, and one of growing interest and significance. At Caltech this month its importance is reflected in the dedication of the new Mabel and Arnold Beckman Laboratories of Behavioral Biology. And that event is underscored by this special issue of *E&S*, which presents articles by seven members of the faculty about their research in this field.

The Beckman Laboratories—in which about 80 faculty members, postdoctoral fellows, research associates, graduate students, and technicians will do research and teaching in behavioral biology—are located on the west side of the Beckman Auditorium mall. Externally, the building

is a twin of the Donald E. Baxter, M.D., Hall of the Humanities and Social Sciences on the east side of the mall. Inside, of course, Beckman and Baxter are not at all alike. Beckman has offices, laboratories, and data preparation and storage rooms for each of nine research units. In addition, there are laboratories, an instrument room, a central stock room, and a sterilization room which will be shared. When the laboratories are in full operation, the faculty and students working there will be making studies of perception, developmental psychology, comparative psychology and ethology, neuroanatomy, neurophysiology, neurochemistry, psychopharmacology, physiological psychology, and experimental psychology.

The objective of such study, says Robert Sinsheimer, chairman of the division of biology, is “to apply the disciplines of the natural sciences to achieve understanding of the biological foundations for animal and, ultimately, human behavior. . . . The origins of human motivation and aggression, of mental illness, of some forms of criminal and other antisocial behavior, and the processes of education and learning are among the areas that might be illuminated.”

The achievement of such goals is in the future, but the work has begun. The seven authors of the articles in this issue—Seymour Benzer, James Olds, Anthonie Van Harreveld, C.A.G. Wiersma, Richard Russell, Roger Sperry, and John Pettigrew—are all distinguished scientists in the field. Among them there are six PhD's, two MD's, and two DSc's, and their work at the Institute alone totals more than 112 years. While they are by no means the only people at Caltech whose work can be called behavioral biology, they represent a cross-section of approaches to this expanding field, and a broad spectrum of experience that can only be suggested in these brief biographical notes:

### Seymour Benzer

Seymour Benzer, professor of biology, began his scientific career as a physicist, and got his PhD at Purdue University in 1947. Almost immediately he became interested in the application of physical concepts to biological problems—using viruses as model systems for gene replication. In 1971 he received a Lasker award for work in this field—research that is generally credited with establishing the foundations of the field of fine-structure genetics. In the mid-1960's Benzer's interest in the possibility of applying molecular biology to the problems of brain function and his curiosity about the genetic control of behavior led him to shift his scientific sights to behavioral biology. He came to Caltech to work with Roger Sperry in 1965, and since 1967 has been making studies of development and behavior in the fruit fly *Drosophila*.



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### James Olds

James Olds, Bing Professor of Behavioral Biology, is a 1947 graduate of Amherst and has a PhD in psychology from Harvard. After graduation he held research appointments at Harvard, McGill, and UCLA, and in 1957 became a member of the faculty at the University of Michigan. In 1969 he came to Caltech and in 1970 was appointed to the Bing professorship. Early in his career Olds discovered "pleasure centers" in the brains of rats—a significant step toward understanding the basic physiological events underlying motivation. More recently, he has been interested in neuronal factors and circuitry in the brain. He has developed a technique to pinpoint memory storage areas there by monitoring individual neurons in the act of learning, and has found evidence that memory storage sites exist in a least four different parts of the brain.



### Anthonie Van Harreveld



Anthonie Van Harreveld, professor of physiology, is a native of Haarlem, the Netherlands. He attended Amsterdam University and received four degrees there between 1925 and 1931—BA, MA, PhD, and MD. He was also an assistant at the university from 1926 to 1932, and served as chief assistant at Utrecht University from 1932 to 1934. In 1934, Van Harreveld came to Caltech as a research assistant, and he has been a member of the staff here ever since. Mammalian physiology—the ultrastructure of nervous tissue, water and electrolyte distribution in the central nervous system, and acute and chronic effects of oxygen deprivation on nervous functions—has been his chief research interest. In addition to his work at Caltech, in 1943 he also served as a consultant in psychiatry at Los Angeles County General Hospital and in 1944 was a research associate in psychiatry and surgery at the University of California.

### C. A. G. Wiersma

C. A. G. Wiersma, professor of biology, is also from the Netherlands. He attended the University of Leiden, receiving an AB in 1926, and then went to the University of Utrecht for an MS in 1929 and a PhD in 1933. He was a chief assistant in medical physiology (a position roughly equivalent to a senior research fellow in the American academic hierarchy) at Utrecht from 1932 to 1934, and then came to Caltech as an associate professor. In the ensuing 39 years, he has learned a lot about the freshwater crayfish; he and the neurophysiology group at the Institute have been investigating its nervous system—and that of other invertebrates—for most of that time. He also spent the seven years from 1943 to 1950 as a member of the attending staff of Los Angeles County General Hospital, and made studies of the myography and treatment of infantile paralysis and the treatment of schizophrenia with electro-narcosis.



*continued on page 36*

# Behavioral Biology at Caltech

Now perhaps—at long last—  
natural science can begin to join the  
ancient quest to understand ourselves

To educate: to train, discipline, or form.

Caltech educates. It seeks “to train, discipline, or form”—to cultivate—the minds of its students. To do so it exposes them, through visual or oral communication, to the minds of its faculty and visiting scholars, to the knowledge in its libraries, to the unknown as probed in its laboratories and observatories.

But what occurs when a mind is trained, disciplined, or formed? Though we do educate, physically or biologically we know not what we do. With all the devices of natural science no one could distinguish the physical living brain of an illiterate from that of a Caltech graduate. We cannot detect a memory or an image; we cannot perceive terror or courage; we can see no trace of *imagination*, no track of conscience.

And we consider this an “age of science.”

Education is but one form of (especially human) behavior. All biological organisms exhibit behavior—they perceive and respond to at least some modes of environmental change. Behavioral biology seeks to analyze and understand the processes underlying the observed behavior.

In the more complex and differentiated organisms, with several modes of perception and many possibilities of response, the integration of behavior is performed by a special set of richly interconnected, electrically active cells—the neurons. A single neuron can perform a complex integration of the information impinging upon it: the potentials of a network or a plexus of neurons are even more intricate.

In these special aggregates of cells lies also the potential for the deposition and retrieval of memory; for that reorganization of memory we call thought and imagination; and—far beyond our present understanding—for the generation of sensation, emotion, and conscious awareness—indeed, for all the varied traits of humanity.

The organization of these aggregates of cells is clearly of

central importance. How does it arise, and according to what principles? The answers that now begin to emerge indicate two principal, interacting determinants of organization—genetic pattern and (particularly, early) environmental influence. The genetic pattern determines the initial matrix and thereby the ultimate potential; early experience enables the organism to select and re-inforce those organizational patterns that lead to adaptive response. In man, particularly, the process appears to be cumulative and (for some years) open, in that selection of the appropriate organizational pattern progressively generates new possibilities of organization in a definable order. And, in man particularly, culture determines the nature of an “adaptive” response.

But these concepts merely frame the central questions: What organization, initial and adaptive, enables us to form an internal representation, an image, of the world about us? What limitations does this organization impose upon the validity of that image? In neuronal terms what does it then mean to know? What does it mean to want, to sense, to fear, to love? How are the diverse activities integrated into a functional unit? What differentiates the metastable states of organization—wakefulness, sleep, dreaming, et al? How does conscious experience arise and what is its role? Are there limits to our capacity to comprehend ourselves? Can we shape a mirror to the mind such that we can understand its reflections?

In our behavioral biology program we have begun to pose these questions. In these pages you will read of probing experiments: into the integration of diverse sensory inputs; into the widespread reorganization of brain pathways when an animal learns; into the microscopic changes that may underlie the formation of a memory; into the genetic specifications of the innate circuitry basic to behavior; into the effects of early visual experience upon subsequent cortical capabilities; into the diversification of function among the component sectors of the human brain.

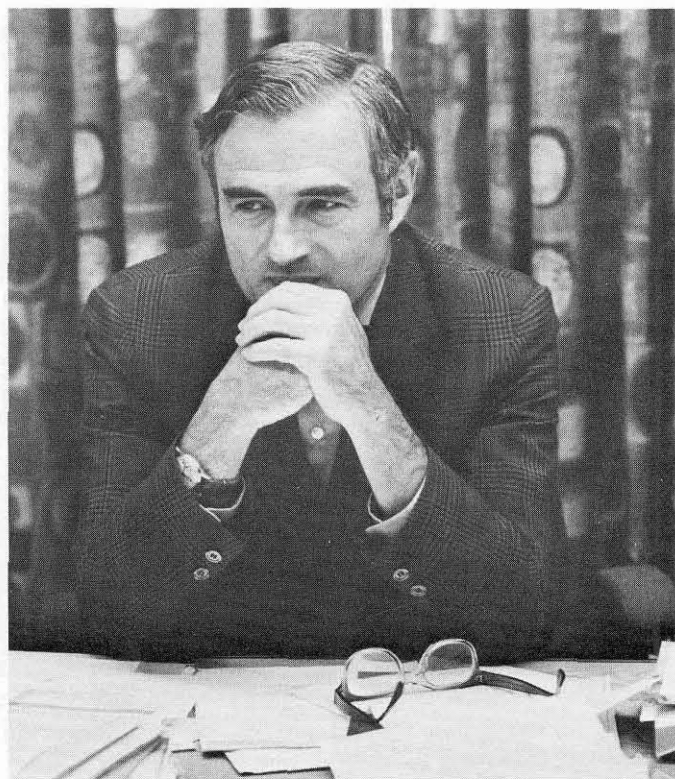
Within the new Mabel and Arnold Beckman Laboratories

of Behavioral Biology we propose to expand and extend this research: to follow up the promising leads and exciting hypotheses as they emerge; to build, in the solid and cumulative style of science, an understanding of the physical bases of behavior and mind.

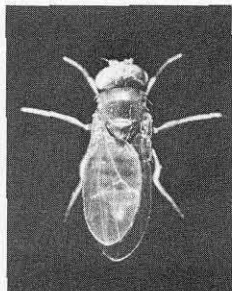
We should not expect quick success in this effort. The task is formidable and may indeed be comparable in magnitude to all that science has so far achieved.

*But now perhaps, at long last, natural science can begin to join the ancient quest to understand ourselves—and thereby begin to illuminate the inner and deeper concerns of humanity.*

*—Robert L. Sinsheimer  
Chairman of the Division of Biology*







# Where Behavior Begins

**The genes, which so largely determine anatomical and biochemical characteristics, must surely interact with the environment to determine behavior. But how?**

When the individual organism develops from a fertilized egg, the one-dimensional information arrayed in the linear sequence of the genes on the chromosomes controls the formation of a two-dimensional cell layer that folds to give rise to a precise three-dimensional arrangement of sense organs, central nervous system, and muscles. Those elements interact to produce the organism's behavior, a phenomenon whose description requires four dimensions at least. Surely the genes, which so largely determine anatomical and biochemical characteristics, must also interact with the environment to determine behavior. But how? In our group at Caltech, we have been applying tools of genetic analysis in an attempt to trace the emergence of multi-dimensional behavior from the one-dimensional gene.

Our objectives are to discern the genetic component of a behavior, to identify it with a particular gene, and then to determine the actual site at which the gene influences behavior and learn how it does so. In brief, we keep the environment constant, change the genes, and see what happens to behavior. Our choice of an experimental organism was constrained by the fact that the simpler an organism is, the less likely it is to exhibit interesting behavioral patterns that are relevant to man; the more complex it is, the more difficult it may be to analyze and the longer it takes. The fruit fly *Drosophila melanogaster* represents a compromise. In mass, in number of nerve cells, in amount of DNA, and in generation time it stands roughly halfway on a logarithmic scale between the colon bacillus *Escherichia coli* (which can be regarded as having a one-

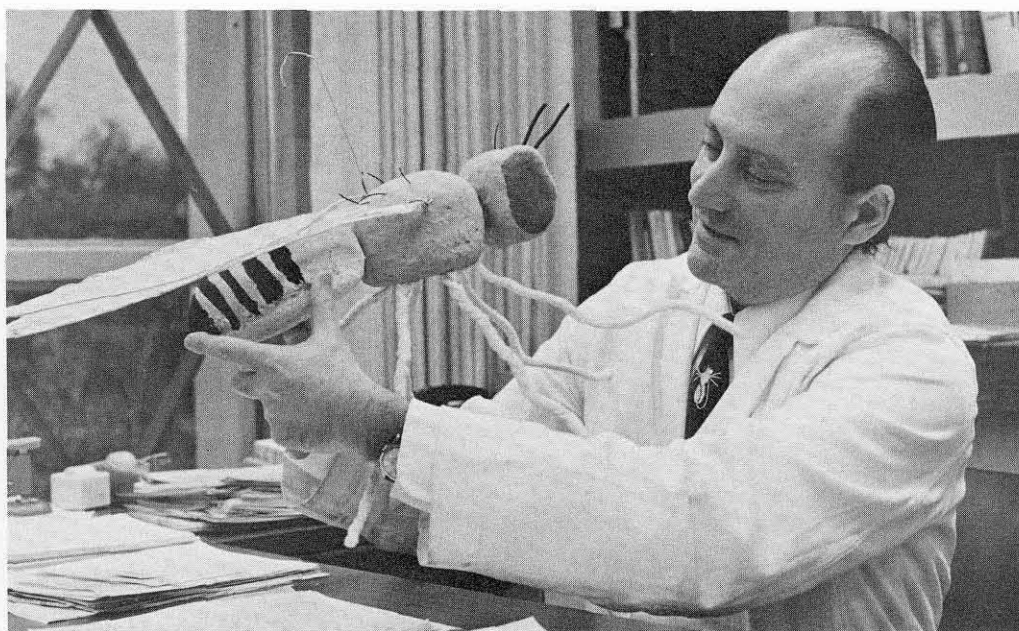
neuron nervous system) and man. Although the fly's nervous system is very different from the human system, both consist of neurons and synapses and utilize transmitter molecules, and the development of both is dictated by genes. A fly has highly developed senses of sight, hearing, taste, smell, gravity, and time. It cannot do everything we do, but it does some things we cannot do, such as fly and stand on the ceiling; its visual system can detect the movement of the minute hand on a clock.

One must not underestimate the little creature, which is not an evolutionary antecedent of man but is itself high up on the invertebrate branch of the phylogenetic tree. Its nervous system is a miracle of microminiaturization, and some of its independently evolved behavior patterns are not unlike our own. For analyzing the relation of specific genes to behavior, it is best to begin with a highly inbred, genetically uniform strain of flies and change the genes one at a time. This is done by inducing a mutation—an abrupt gene change that is transmitted to all subsequent generations.

A population of flies exposed to a mutagen (radiation or certain chemicals) yields some progeny with anatomical anomalies such as white eyes or forked bristles, and it also yields progeny with behavioral abnormalities. Workers in many laboratories (including ours) have compiled a long list of such mutants, each of which can be produced by the alteration of a single gene.

Let me use a defect in visual behavior to illustrate in some detail how we analyze behavior. The first problem is to quantitate behavior and to detect and isolate

BY SEYMOUR BENZER



Seymour is not the only Benzer with an interest in the fruit fly. His daughter Martha made this way-more-than-life-size model several years ago for a junior high school science project.

behavioral mutants. It is possible to handle large populations of flies, treating each individual much as a molecule of behavior and fractionating the group into normal and abnormal types. We begin—using the technique devised by Edward B. Lewis, Thomas Hunt Morgan Professor of Biology at Caltech—by feeding male flies sugar water to which has been added the mutagen ethyl methane sulfonate, an alkylating agent that induces mutations in the chromosomes of sperm cells. The progeny of mutagenized males are then fractionated by means of a kind of countercurrent distribution procedure, somewhat as one separates molecules into two liquid phases. Here the phases are light and darkness, and the population is “chromatographed” in two dimensions on the basis of multiple trials for movement toward or away from light. Normal flies—and most of the progeny in our experiment—are phototactic, moving toward light but not away from it. Some mutants, however, do not move quickly in either direction; they are *sluggish* mutants. There are *runners*, which move vigorously both toward and away from light.

A *negatively phototactic* mutant moves preferentially away from light. Finally, there are the *nonphototactic* mutants, which show a normal tendency to walk but no preference for light or dark. They behave in light as normal flies behave in the dark, which suggests that they are blind.

My colleague Yoshiki Hotta, who is now at the University of Tokyo, and I studied the electrical response of the *nonphototactic* flies’ eyes and found that in one of the mutants the photoreceptor cells are normal in the young adults but that they degenerate with age. There are genetic

conditions that produce this result in humans, and it may be that the fly’s eye can provide a model system for studying certain kinds of blindness.

Now, if one knows that a certain behavior (*nonphototactic*, say) is produced by a single-gene mutation and that it seems to be explained by an anatomical fault (the degenerated receptors), one still cannot say with certainty what is the primary “focus” of that genetic alteration—that is, the site in the body at which the mutant gene exerts its primary effect. The site may be far from the affected organ. Certain cases of retinal degeneration in man, for example, are due not to any defect in the eye but to ineffective absorption of vitamin A from food in the intestine. In order to trace the path from gene to behavior one must find the true focus at which the gene acts in the developing organism. How? A good way to trouble-shoot in an electronic system—a stereophonic set with two identical channels, for example—is to interchange corresponding parts. That is in effect what we do with *Drosophila*. Rather than surgically transplanting organs from one fly to another, however, we use a genetic technique. We make mosaic flies, composite individuals in which some tissues are mutant and some have a normal genotype. Then we look to see just which part has to be mutant in order to account for the abnormal behavior.

One method of generating mosaics depends on a strain of flies in which there is an unstable ring-shaped X chromosome. Flies, like humans, have X and Y sex chromosomes; if a fertilized egg has two X chromosomes in its nucleus, it will normally develop into a female fly; an XY egg yields a male. In *Drosophila* it is the presence of two

X chromosomes that makes a fly female; if there is only one X, the fly will be male. The ring X chromosome has the property that it may get lost during nuclear division in the developing egg, so that some tissues retain only one X chromosome while others have both.

Such a mosaic fly is a system in which the effects of normal and of mutant genes can be distinguished in one animal. We arrange things so that both a behavioral gene and “marker” genes are combined on the same X chromosome. This is done through the random workings of the phenomenon of recombination, in which segments of two chromosomes (in this case the X) “cross over” and exchange places with each other during cell division in the formation of the egg. In this way we can, for example, produce a strain of flies that are *nonphototactic* and also have white eyes (instead of the normal red) and a yellow body color. Then we breed males of this strain with females of the ring X strain. Some of the resulting embryos will have one ring X chromosome and one mutation-loaded X chromosome. In a fraction of these embryos the ring X (carrying normal genes) will be lost at an early nuclear division. The XX body parts of the resulting adult fly will have one X chromosome with normal genes and one with mutations; because both the behavioral and the anatomical genes in question are recessive (their effect is masked by the presence of a single normal gene), the mutations will not be expressed in those parts. In the body parts having lost the ring X, however, the single X chromosome will be the one carrying the mutations. And because it is all alone, the mutations will be expressed. Examination of the fly identifies the parts that have normal color and those in which the mutant genes have been uncovered. We can select, from among the randomly divided gynandromorphs, individuals in which the dividing line falls in various ways: a normal head on a mutant body, a mutant head on a normal body, a mutant eye and a normal one, and so on. And then we can pose the question we originally had in mind: What parts must be mutant for the mutant behavior to be expressed?

When Hotta and I did that with certain visually defective mutants—for instance ones that produce no receptor potential—we found that the electroretinogram of the mutant eye was always completely abnormal, whereas the normal eye functioned properly. Even in gynandromorphs in which everything was normal except for one eye, that eye showed a defective electroretinogram. This makes it clear that the defects in those mutants are not of the vitamin A type I mentioned before; the defect must be autonomous within the eye itself.

In these mutants the primary focus of the *phototactic* defect is in the affected organ itself. More frequently, however, the focus is elsewhere. A good way to see how this situation is dealt with is to consider a *hyperkinetic*

## A fly has highly developed senses of sight, hearing, taste, smell, gravity, and time

mutant that was studied by William D. Kaplan and Kazuo Ikeda at the City of Hope Medical Center. When such a fly is anesthetized with ether, it does not lie still but rather shakes all six of its legs vigorously. Flies that are mosaics for the gene shake some of their legs but not others, and the shaking usually correlates well with the leg's surface genotype as revealed by markers—but not always. The point is that the markers are on the outside of the fly. The genotype of the surface is not necessarily the same as that of the underlying tissues, which arise from different regions of the embryo. And one might well expect that leg function would be controlled by nervous elements somewhere inside the fly's body that could have a different genotype from the leg surface. The problem is to find a way of relating internal behavioral foci to external landmarks. Hotta and I developed a method of mapping this relation by extending to behavior the idea of a “fate map,” which was originally conceived by A. H. Sturtevant, professor of biology at Caltech from 1928 until his death in 1970.

When Hotta and I undertook to map behavior in *Drosophila*, we began by preparing our own fate map of the adult external body parts based on the scores for 703 mosaic flies. Distances on the map are in “sturts,” a unit that John Merriam, Hotta, and I have proposed in memory of Sturtevant. One sturt is equivalent to a probability of 1 percent that the two structures will be of different genotypes.

Now back to *hyperkinetic*. We produced 300 mosaic flies and scored each for a number of surface landmarks and for the coincidence of marker mutations at those landmarks with the shaking of each leg. We confirmed that the behavior of each leg (whether it shakes or not) is independent of the behavior of the other legs and that the shaking behavior and the external genotype of a leg are frequently the same—but not always. The independent behavior of the legs indicated that each had a separate focus. For each leg we calculated the distance from the shaking focus to the leg itself and to a number of other landmarks and thus determined a map location for each focus. They are near the corresponding legs but below them, in the region of the blastoderm identified by embryological studies as the origin of the ventral nervous system. This is consistent with electrophysiological evidence that neurons in the thoracic ganglion of the ventral nervous system behave abnormally in these mutants.

Another degree of complexity is represented by a mutant

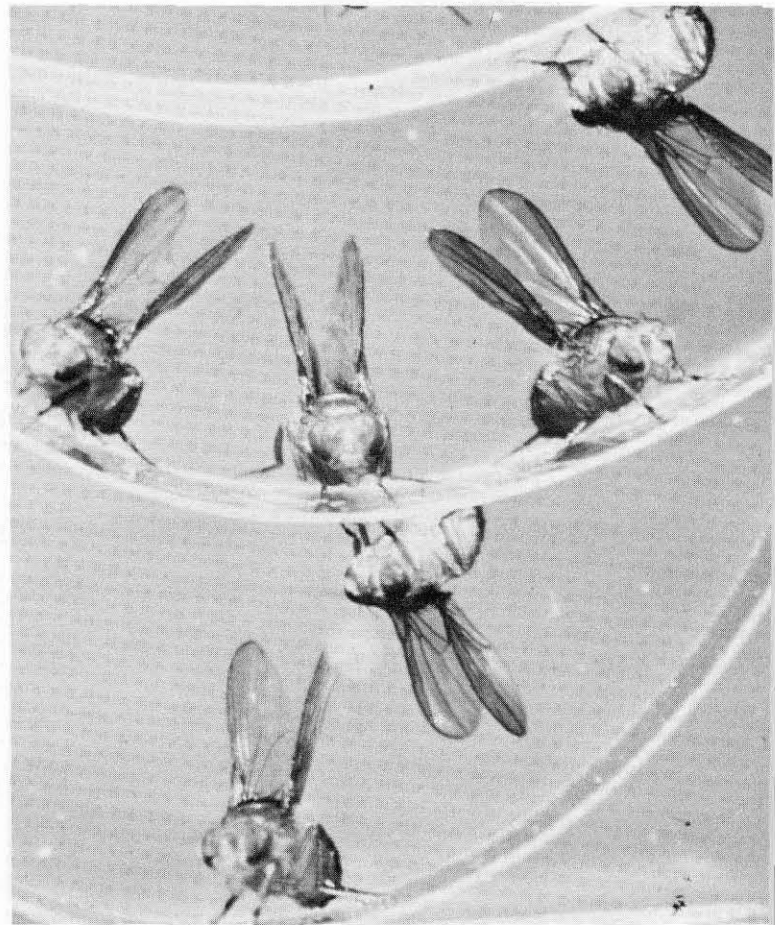


we call *drop-dead*. These flies develop, walk, fly, and otherwise behave normally for a day or two after eclosion. Suddenly, however, an individual fly becomes less active, walks in an uncoordinated manner, falls on its back, and dies; the transition from apparently normal behavior to death takes only a few hours. The time of onset of the syndrome among a group of flies hatched together is quite variable; after the first two days the number of survivors in the group drops exponentially, with a half-life of about two days. It is as if some random event triggers a cataclysm. The gene has been identified as a recessive one on the X chromosome. Symptoms such as these could result from malfunction almost anywhere in the body of the fly, for example from a blockage of the gut, a general biochemical disturbance, or a nerve disorder. In order to localize the focus we did an analysis of 403 mosaics in which the XX parts were normal and the X body parts expressed the *drop-dead* gene and the surface-marker mutations, and we scored for *drop-dead* behavior and various landmarks.

*Drop-dead* behavior, unlike shaking behavior, which could be scored separately for each leg, is an all-or-none property of the entire fly. First we did a rough analysis to determine whether the behavior was most closely related to the head, thorax, or abdomen, considering only flies in which the surface of each of these structures was either completely mutant or completely normal. Among mosaics in which the entire head surface was normal almost all behaved normally, but 6 flies out of 97 died in the *drop-dead* manner; in the reciprocal class 8 flies of 80 with mutant head surfaces lived. In other words, the focus was shown to be near to, but distinct from, the blastoderm site of origin of the head surface. Similar analysis showed that the focus was substantially farther away from the thorax and farther still from the abdomen. Next we considered individuals with mosaic heads. In certain visual mutants the visual defect was always observed in the eye on the mutant side of the head; flies with half-normal heads had normal vision in one eye. For *drop-dead*, on the other hand, of mosaics in which half of the head surface was mutant only about 17 percent dropped dead. All the rest survived.

Now, a given internal part should occur in normal or mutant form with equal probability, as the external parts in these mosaics did. On that reasoning, if there were a single focus inside the head of the fly, half of the bilateral-mosaic flies should have dropped dead. We formed the hypothesis, therefore, that there must be two foci, one on each side, and that they must interact. Both of them must be mutant for the syndrome to appear. In other words, a mutant focus must be "submissive" to a normal one. In that case, if an individual exhibits *drop-dead* behavior, both foci must be mutant, and if a fly survives, one focus may be normal or both of them may be.

(From "Genetic Dissection of Behavior" by Seymour Benzer. Copyright December 1973 by Scientific American, Inc. All rights reserved. (Photo by Fritz Goro.)



"Wings-up" flies are mutants that keep their wings straight up and cannot fly—behavior that might possibly be the result of flaws in wing structure, in musculature, or in nerve function. Hotta and Benzer's experiments have traced the defect to the muscle.

Mapping a bilateral pair of interacting foci calls for special analysis. By considering the various ways a mosaic dividing line could fall in relation to a pair of visible external landmarks (one on each side of the body) and a symmetrical pair of internal foci, one can set up equations based on the probability of each possible configuration. Using the observed data on how many mosaic flies showed the various combinations of mutant and normal external landmarks and mutant or normal behavior, it is possible to solve these equations for the map distance from each landmark to the corresponding focus and from one focus to the homologous focus on the other side of the embryo. The *drop-dead* foci turn out to be below the head-surface area of the blastoderm, in the area embryologists have assigned to the brain. Sure enough, when we examined the brain tissue of flies that had begun to exhibit the initial stages of *drop-dead* behavior, it showed striking signs of degeneration, whereas brain tissue fixed before the onset of symptoms appeared normal. As for mosaics whose head surfaces are half-normal, those that die show degeneration of the brain on

both sides; the survivors' brains show no degeneration on either side, a finding consistent with the bilateral-submissive-focus hypothesis. It appears that the normal side of the brain supplies some factor that prevents the deterioration of the side with mutant focus.

The mutants so far mapped provide examples involving the main components of behavior: sensory receptors, the nervous system, and the muscles. For some of the mutants microscopic examination has revealed an obvious lesion of some kind in tissue. Clearly the question is whether or not fate mapping is necessary; why do we not just look directly for abnormal tissue? One answer is that for many mutants we do not know where to begin to look, and it is helpful to narrow down the relevant region. Furthermore, in many cases no lesion may be visible, even in the electron microscope. More important, and worth reiterating, is the fact that the site of a lesion is not necessarily the primary focus. For example, an anomaly of muscle tissue may result from a defect in the function of

## **We have begun to study more elaborate behavior such as circadian rhythm, sexual courtship, and learning**

nerves supplying the muscle. This possibility has been a lively issue in the study of diseases such as muscular dystrophy.

Another application of mosaics is in tagging cells with genetic labels to follow their development. The compound eye of *Drosophila* is a remarkable structure consisting of about 800 ommatidia—unit eyes containing eight receptor cells each. The arrangement of cells in an ommatidium is precise and repetitive; the eye is in effect a neurological crystal in which the unit cell contains eight neurons. Thomas E. Hanson, Donald F. Ready, and I have been interested in how this structure is formed. Are the eight photoreceptor cells derived from one cell that undergoes three divisions to produce eight, or do cells come together to form the group irrespective of their lineage? This can be tested by examining the eyes of flies, mosaic for the *white* gene, in which the mosaic dividing line passes through the eye. By sectioning the eye and examining ommatidia near the border between white and red areas microscopically, it is possible to score the tiny pigment granules that are present in normal photoreceptor cells but absent in *white* mutant cells. The result is clear: A single ommatidium can contain a mixture of receptor cells of both genotypes. This proves that the eight cells cannot be derived from a single ancestral cell but have become associated in their special group of eight irrespective of lineage. The same conclusion applies to the other cells in each ommatidium, such as the normally heavily pigmented cells that surround the receptors.

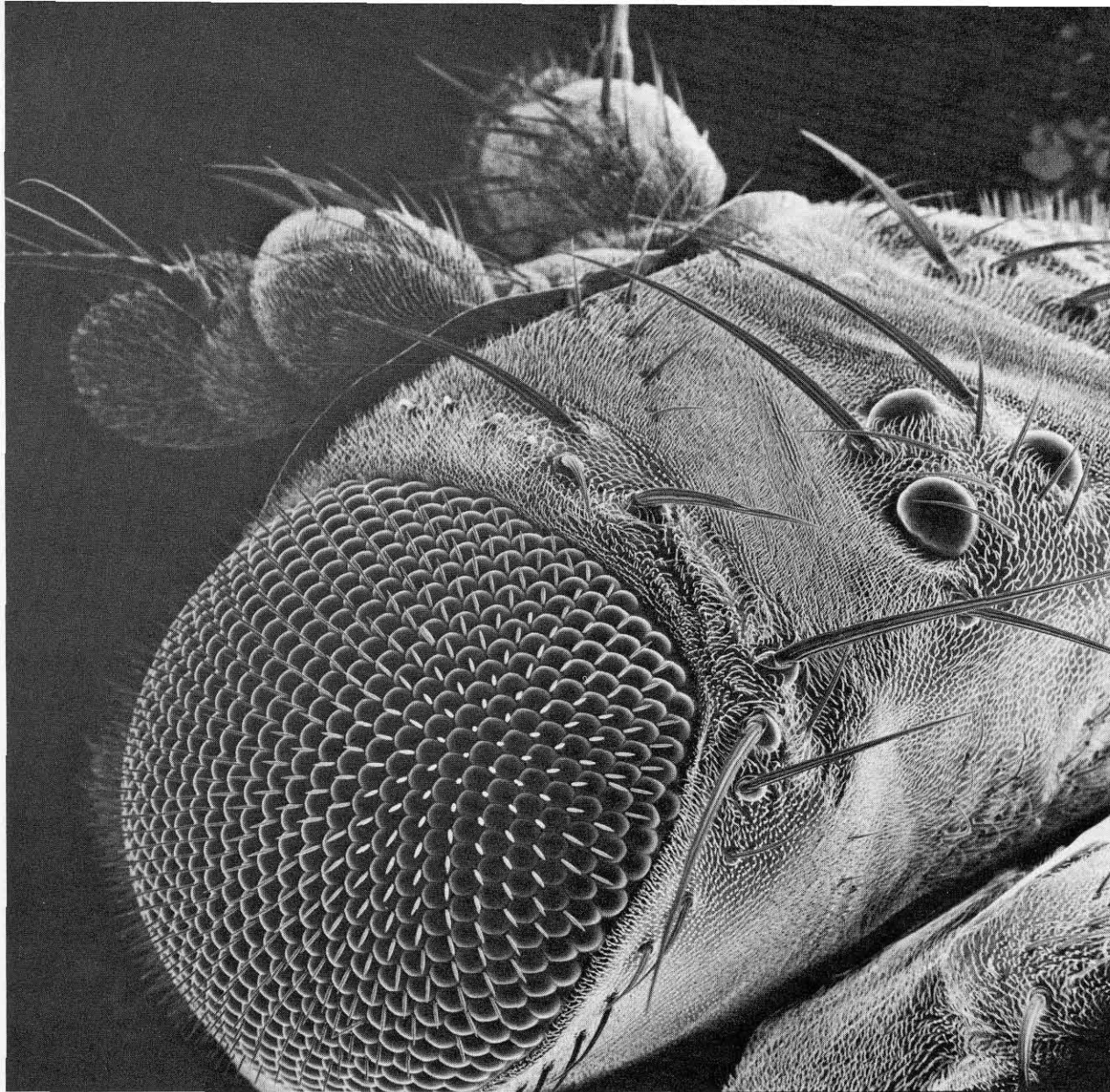
Not all cells have such convenient pigment markers. It would obviously be valuable to have a way of labeling all the internal tissues as being either mutant or normal, much as yellow color labels a landmark on the surface. This can now be done for many tissues by utilizing mutants that lack a specific enzyme. If a recessive enzyme-deficient mutant gene is recombined on the X chromosome along with the *yellow*, *white*, and behavioral genes, and mosaics are produced in the usual way, the male tissues of the mosaic will lack the enzyme. By making a frozen section of the fly and staining it for enzyme activity one can identify normal mutant cells.

In order to apply this method in the nervous system one needs to have an enzyme that is normally present there in a large enough concentration to show up in the staining procedure and a mutant that lacks the enzyme, and the lack should have a negligible effect on the behavior under study. Finally, the gene in question should be on the X chromosome. Douglas R. Kankel and Jeffrey C. Hall in our group have developed several such mutants. By scoring the internal tissues they have constructed a fate map of the internal organs of the kind made earlier for surface structures. We are now adapting the staining method for electron microscopy in order to work at the level of the individual cell.

Much of what has been done so far involves relatively simple aspects of behavior chosen to establish the general methodology of mutants and mosaic analysis. Can the methodology be applied to more elaborate and interesting behavior such as circadian rhythm, sexual courtship, and learning? Some beginnings have been made on all of these. By making flies that are mosaic for normal and mutant rhythms, Konopka has shown that the internal clock is most closely associated with the head. Looking at flies with mosaic heads, he found that some exhibited the normal rhythm and others the mutant rhythm but that a few flies exhibited a peculiar rhythm that appears to be a sum of the two, as if each side of the brain were producing its rhythm independently and the fly responded to both of them. By applying the available cell-staining techniques it may be possible to identify the cells that control the clock.

Sexual courtship is a higher form of behavior, since it consists of a series of fixed-action patterns, each step of which makes the next step more likely. The sex mosaics we have generated lend themselves beautifully to the analysis of sexual behavior. A mosaic fly can be put with normal females, and its ability to perform the typical male courtship steps can be observed. Hotta, Hall, and I found that the first steps (orientation toward the female and vibrating of the wings) map to the brain. This is of particular interest because the wings are vibrated by motor nerve impulses from the thoracic ganglion; even a female ganglion will produce the vibration "song" typical





*Drosophila melanogaster*—as seen by the scanning electron microscope. This is a photograph of the fly's head, and the most prominent feature is the large compound eye—a re-

markable structure consisting of 800 unit eyes, or ommatidia. Antennae are at the upper left, and the three globular objects on the right are simple eyes, or ocelli.

of the male if directed to do so by a male brain. It would appear that the thoracic ganglion in a female must “know” the male courtship song even though she does not normally emit it.

Sexual behavior in *Drosophila*, although complex, is a stereotyped series of instinctive actions that are performed correctly by a fly raised in isolation and without previous sexual experience. Other forms of behavior such as phototaxis also appear to be already programmed into the fly when it ecloses. Whether a fruit fly can learn has long been debated; various claims have been made and later shown to be incorrect. Recently William G. Quinn Jr. and William A. Harris in our laboratory have shown in carefully controlled experiments that the fly can learn to avoid specific odors or colors of light that are associated with a negative reinforcement such as electric shock. This opens the door to genetic analysis of learning behavior through mutations that block it.

In tackling the complex problems of behavior the gene provides, in effect, a microsurgical tool with which to produce very specific blocks in a behavioral pathway. With temperature-dependent mutations the blocks can be turned on and off at will. Individual cells of the nervous system can be labeled genetically, and their lineage can be followed during development. Genetic mosaics offer the equivalent of exquisitely fine grafting of normal and mutant parts, with the entire structure remaining intact. What we are doing in mosaic mapping is in effect “unrolling” the fantastically complex adult fly, in which sense organs, nerve cells, and muscles are completely interwoven, backward in development, back in time to the blastoderm, a stage at which the different structures have not yet come together. Filling the gaps between the one-dimensional gene, the two-dimensional blastoderm, the three-dimensional organism, and its multidimensional behavior is a challenge for the future. □



# The Creation of Learning and Memory

BY JAMES OLDS

## Understanding Education

The human brain is above all an educatable machine. For this naturally selected computer we have a set of cultural programs that have been perfected over the centuries by a kind of dog-eat-dog competition between ideas and societies. Sad to say, we still do not understand either the basic machine or the programs, though we are continually called upon to make patches to overcome obvious deficiencies.

Eugenicists offer to solve the range of our problems by supplying us with a new and better computer—the genetically planned human—but there are reasons why this answer is not sufficient. One is the danger of losing from the pool of genes some that might be needed later for reasons not known to us now. Another is that people are irrationally attached to their genes.

The alternative is teaching, education—programming, if you like. In the past we have been lucky; each national culture has pressed forward, improving its educational tools by repeatedly choosing the winner in a battle of ideas, and eliminating the ones that did not do well. Our sense of how to educate came not from understanding but from success.

But to solve new problems rationally we want understanding; it is a natural urge that we cannot stifle. One course is to seek a sensible theory of brain function, which should illuminate to some degree the basic quandaries of education. What are these quandaries? The first has to do with punishment. Does punishment guide behavior in organized pathways; or does it make neuroses and suppress creativity? We really do not know much about what kind of learning profits by punishment and what kind is better off without it. Human “imprinting” is another quandary. The church, for example, used to worry a good deal about the rote-fare a child was exposed to prior to the age of reason. Now, those who control the radio and TV assure us that this is no problem. We really do not know what the steps are in building the early “systems programs” for the human being. Mothering the very young at all hours is a third quandary. It is offered by some as a prescription for the child’s eventual mental health. But others answer that a mother who divides her time sensibly among her work,

her grown-up pleasures, and her children is better off from the point of view of her own mental health—and thus better for her children. We really know very little about the influences of a mother’s contacts, her gestures, her early words, and other such things.

When we get children into school, there are more questions. How should we teach? How much reading? How much feedback? How much repetition? How can we keep the child interested? How can we force him to do what he needs to do to live a full and happy life? What kind of grading system? What kind of rewards and penalties? How much praise and blame? How much homework? How often, if ever, should a child “fail”?

I could make another list of questions for education in employer-employee relations, or in adult interaction (mutual education). In the end we are all programmers of people.

## Underlying Problems

A web of basic scientific questions lies just under the surface of these practical problems. If we could frame the questions properly, we would have taken an organizing step toward a good theory. We cannot. But we do know something about them.

In dealing with these questions we are interested in the creation of memories—different kinds for different purposes. We are interested in making some memories durable (values, perhaps) and some transient (anxiety, for example). We are interested in making some memories readily accessible so that they are available for repeated use in the course of the day. We are interested in the interaction of memories—so that they do not upset one another; and so that some (like systems programs) serve an organizing function in relation to others. And, finally, we recognize the overriding importance of the problems of interest, attention, sanction, motive.

Our studies are aimed at the problems of memory, learning, and motivation of learning at the most basic level. We are trying to find what the basic organization of the brain has to tell us. Our primary aim is not to find answers to the practical questions but to find organizing

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ideas that will inject wisdom into our search for those answers.

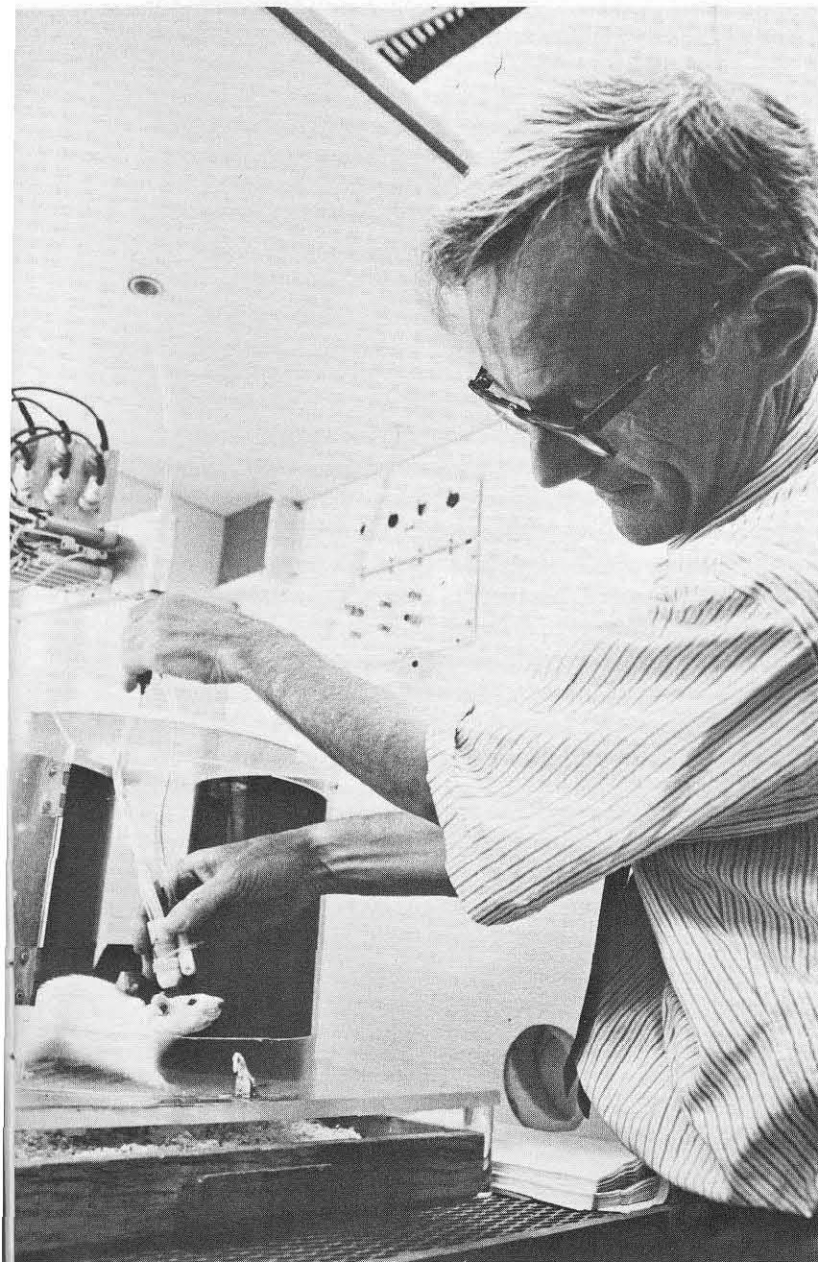
Our interest is in the human brain, but we work with the rat because this animal has a miniaturized copy of the human brain. Many of the major parts are the same, both as to internal wiring and to relations between them.

### **What We Do with Rats**

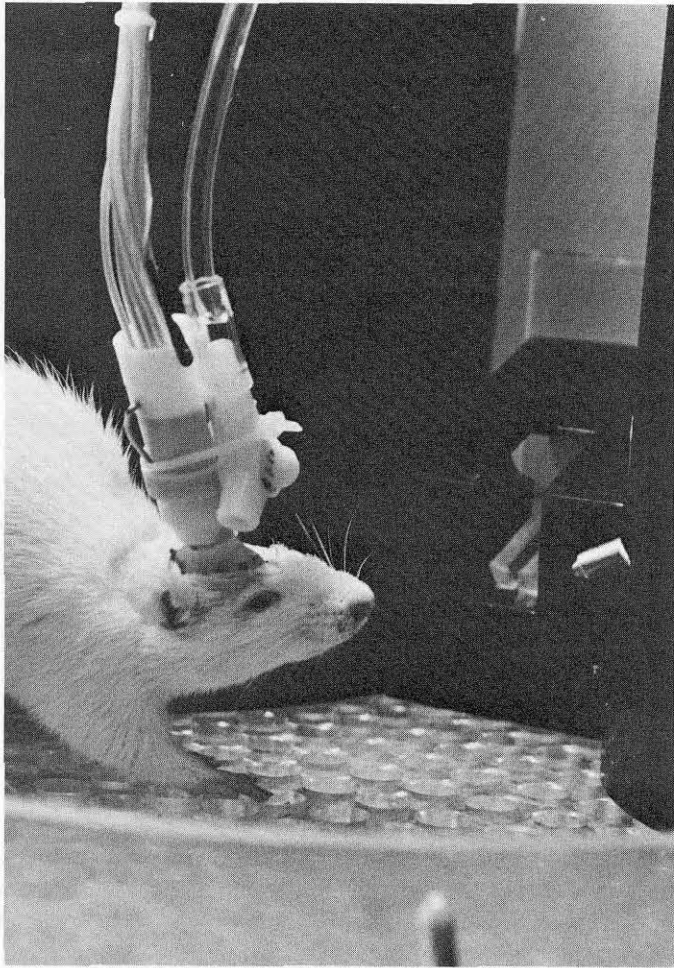
In our experiments, we implant the brains of anesthetized rats with many probes in each brain. When the rats wake up, they are behaviorally active, alert, and ready to play experimenters' games. They are "plugged in," and an "umbilical cord" from the probes carries messages to the computer during the experiments. Rats have a long genetic tradition of doing well even under bizarre conditions, so they quickly come to behave as if they are used to and happy with the cable system.

Our probe-and-cable system is used to record electrically the signals of the neurons in the brains of the rats. Neurons, like crickets, emit repetitive outbursts when they are active. In crickets it is an outburst of clicks; in nerve cells it is an outburst of "electrical spikes." These are picked up by our probes, amplified for display on an oscilloscope, and counted by a computer. The spikes are ongoing, but a stimulus that affects the neuron (such as an auditory signal from a loudspeaker) causes an acceleration or a deceleration, a change in the number of spikes per second. Our probes touch several neurons, but we can distinguish the spikes from each by automatic electrical sorting techniques. We could count the activity of just one neuron; but we are not usually this selective. Usually we count spikes from a small group (six or seven neurons). But this allows us to track the path of an incoming signal in the brain.

Our method is to apply an auditory signal with a sharp onset and to trace the resulting neuronal activity, in successive time frames, through the various stations of the brain. We thus establish a message map of the course of the signal. We first do a control experiment and make a message map for a habituated signal that has become meaningless to the animal. Then we add meaning to the signal by a "Pavlovian conditioning experiment." This is done by presenting food one second after the signal; because the animal is hungry, the auditory signal begins to elicit behavior directed to the food. During this period when meaning is added to the auditory signal, we make a series of successive message maps.



James Olds, Bing Professor of Behavioral Biology, makes studies with rats to learn more about the problems of memory, learning, and motivation at the most basic level.



A two-way probe-and-cable system uses sound signals to stimulate neurons in the brain of this rat and record his responses in successive stages of a learning situation. The resulting series of message maps trace the pathway for the formation of a memory. In this case the rat is learning to associate the presentation of food with a sound. There are nine white cables on the left which carry electrical spikes from the different brain probes. The transparent plastic tube on the right carries the auditory signal to the animal. To the right of the animal are the food magazine and the water spout.

By overlaying these successive maps, it is possible to trace out a family of changes that succeed one another during the course of training. And for each of these changes it is possible to gain some indication of where the message branched from its old pathway into a new one as a consequence of the training procedure.

### **Auditory Tuning**

Training caused the signal to branch off into new paths at almost every station of the auditory pathway. It also caused preexisting responses in the auditory centers to be modified, usually to be amplified or enhanced. There was also a substantial change in the background firing rate—the so-called spontaneous discharge rate of neurons in some of the auditory areas.

The amplification of the auditory responses was observed even at the very first brain station of the auditory path; it may also have involved the nerve that joins the ear to the brain. Here, after training, there was often a 30 percent increase in the spike rate caused by the auditory signal. Similar changes occurred at the other stations of the auditory pathway; in the higher centers the changes were proportionally even larger, often increasing by several hundred percent.

Were the response changes in the higher auditory centers caused by the changes in the lower centers—or vice versa? Two features made it difficult to accept the view that the changes in the higher centers were directly caused by those in the lower ones. First, the changes in the higher centers were much larger in proportion to the total response. Second, the changes in different centers often occurred at different stages of training. In some experiments, changes in the lower centers were completed in the first 60 trials of the training, while changes in the middle stations continued into the second and even third sets of 60 trials.

The timing of the responses also made it difficult to accept the view that changes in the lower centers were caused by those in the higher ones. The changed responses in the first auditory station appeared about one or two milliseconds after the tone reached the animal. Thus, there could not have been time for the auditory message to go first up to the cortex to be recognized and from there come back to cause the response in the lower center to be increased. In fact, the message would not even have had time to go to the second auditory station. Therefore, it appeared that the auditory system had to be ready for these signals before they reached the ear. The ear, or at least the first auditory station, was in some way pre-tuned to accept them.

However, a second kind of influence from the upper stations is still possible—a readiness of the lower station for the specific stimulus, maintained by some active process in the cortex (or in the middle stations). Such a process



would be developed by the training procedure, and would always be “on” awaiting the anticipated stimulus. If such a process existed, it would match what psychologists call an active or dynamic memory trace, or a psychological set.

### Dynamic Memory Traces in the Cortex

The suggestion that a dynamic process in the cortex might prepare the auditory pathways led to the question of how such an influence might work and how it could be experimentally identified. A likely mechanism is well known. It is a 3-neuron dynamic switch in which the activity of a control neuron can cut off the flow of information between two other neurons. If control neurons in the cortex brought such “pre-synaptic” inhibition to bear on the lower auditory centers, then a slowing of the background firing rate in the cortex might be one way of preparing the lower centers for a signal. If so, such slowing might be observed during Pavlovian conditioning.

Dr. John Disterhoft, research fellow in biology, looked for changes of this kind. In most of the lower centers, training caused brief and insignificant changes in the background firing rates and left them well within the control range. But in the cortex there was a stable, sustained change in the ongoing discharge pattern, consisting of a 25 percent decline in the average “spontaneous” spike rate of auditory cortex neurons. Both the sustained nature of the change and its downward direction fit the view that these could be control neurons whose firing screened out the auditory signals before training. So one kind of “dynamic memory trace” could be a slowing of control neurons in the cortex resulting in amplification of responses in lower centers.

### Structural Traces in the Cortex

Were these dynamic traces the only memories in the cortex? This seemed unlikely. We therefore sought evidence for other longer-lasting changes of connecting structures. Other investigators had suggested that mushroom-like contact organs (called “spines”) which link neurons might be caused to grow by training procedures. If cortex neurons become more strongly coupled to input signals by the growth of spines during training, they should become more responsive to auditory stimuli. This might form the basis for a test, but the difficulty was that response changes observed in the cortex might also be caused by 3-neuron switches, like those in the lower centers. How could the two kinds of process be separated? The most fruitful idea so far has been to assume that in the case of lasting structural changes a growth process might continue for some time after training stopped. The underlying assumption is that training starts the growth of the spines, but that they continue to grow after training has stopped. To test this idea it was decided to start with an experiment in which behavior not only improved during training, but continued to improve during an extended time-out period. Disterhoft found that if he first trained animals to respond positively

to one auditory signal called the CS+, and to ignore a second auditory signal called CS–, and then reversed the significance of these two, the behavior followed an appropriate course.

After the switch, *behavior* improved in response to the new CS+, and deteriorated in response to the old one. By the end of an eight-hour training series the response to the two signals was at a middle level and about equal. If an eight-hour time-out period was then interpolated, the behavioral response to the *new* CS+ was greatly augmented, and the response to the *old* one had disappeared almost completely.

What changes occurred in the cortex during the time-out interval? The firing-rate response of neurons to the new CS+ that had been initiated by training was substantially augmented by the time-out period, just as was the

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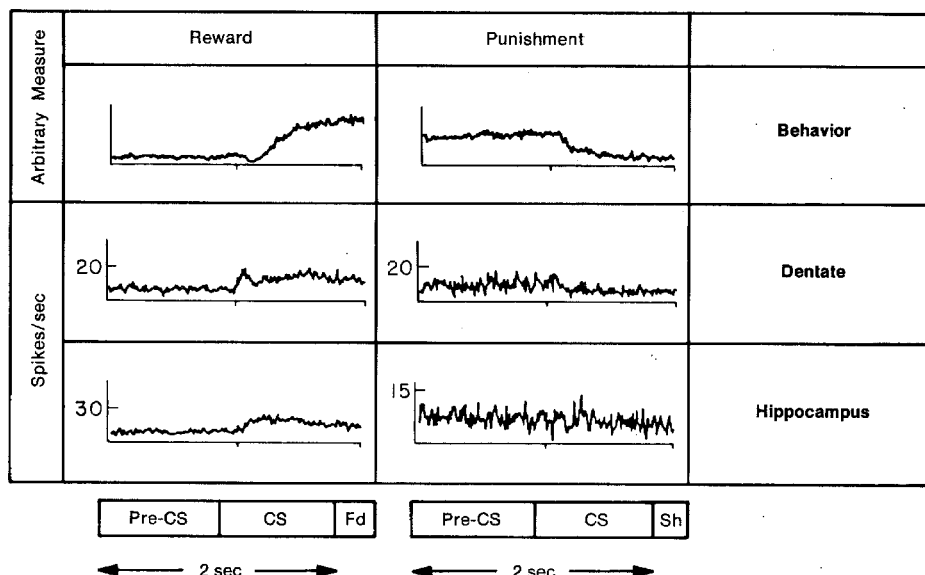
behavioral response. However, the firing-rate response to the old CS+, which had been to some degree diminished during training, surprisingly sprang partly back to life during the time-out.

This was not exactly what we expected because during the time-out the *behavior* had improved to the new CS+ and died out to the old one. But in this period cortex firing-rate activity increased to both the new CS+ and to the old one. Thus, while the cortex changes could account for the behavioral improvement in response to the CS+ during the time-out, it could not account for the equally adaptive behavior loss in response to the CS–

In the same experiment, however, it was possible to observe changes elsewhere that could account for this behavior loss. During the time-out period a reduction in response to the CS– (without any changed response to the CS+) occurred in the neurons of the hippocampus, and in neurons in special “middle” regions of the brain which are thought to be involved in controlling attention. The experiment as a whole therefore suggested that during time-out some structural consolidation of a newly acquired positive response might have occurred in the cortex, and some similar consolidation of “extinction” or suppression might have occurred in the hippocampus or in other regions.

In any event, when changes such as these become improved (rather than disappearing) with the passage of time, the hypothesis that they are caused by some temporary *dynamic* memory process (that could die out) becomes less likely, and the possibility that the growth of a *structure* is involved becomes the more likely.

Average rates before and during a conditioned stimulus (CS) are represented on these curves. They show that the behavior of the animals and the activity of the dentate (motive) units increased in anticipation of food reward (Fd) and decreased in anticipation of a punishing shock (Sh). The activity of the hippocampus units increased in anticipation of food but was not changed at all before the shock. The absence of any change in the hippocampus when the dentate was inhibited suggests that increased dentate activity is necessary before learning occurs in the hippocampus (which is supposed to be one kind of memory system).



### Reinforcement and Learning in the Hippocampus

Reward and punishment enter the problem of learning in many ways. For higher learning, the role of reward is at least twofold. First, reward or some alerting event is required to “turn on the learning machine.” Second, reward enters again to determine what behaviors will be repeated and what ideas will be rehearsed.

The hippocampus is a complicated structure rolled up inside the cortex on each side of the head. The elegant arrangement of its neurons makes it easy and interesting for neuroanatomists to study. The loss of the hippocampus in humans is known to cause a specific loss of one kind of recent memory (for daily lists and events). The hippocampus is connected so as to tie together the processed information from the association cortex with the attentional and motivational centers of the lower brain. This has led to the supposition that it may be involved in critical interactions between motivation and learning.

Experiments in our laboratory by Dr. Menahem Segal, which tracked a conditioned stimulus through the hippocampus, seem to fit this view. One particular family of neurons in the hippocampal system seems to be involved mainly in turning on the hippocampus as a learning machine during training. Then, the order of firing in the fully trained animal is compatible with the view that the same family of neurons is involved again in causing the performance of remembered behaviors.

The main family of neurons in the hippocampus is arranged in a fashion that matches a computer memory grid. Because these neurons also have marked responses to conditioning, we may call them the “memory” neurons. This grid of elements is fed by four different sets of fibers

(possibly bringing information to be remembered). Three of these come from the cortex, the drive system, and the arousal system, respectively. The fourth set comes from a neighboring family of neurons (the dentate granules), whose main input is also from the drive system. We call this fourth set the “motive” set of neurons. The drive-system messages thus have both direct and indirect access to the memory grid, but the main drive information is that relayed through the motive neurons—which send their messages only to the memory grid.

Segal’s experiments suggest that the activity of the motive set is necessary to *turn on* the memory grid—to make it record—and that later, during playback, memories may need to trigger this motive system in order to evoke behavior.

Three findings pointed in this direction. One was that the motive set of neurons learned first. Early in training, the signal came to cause a briefly delayed acceleration in the firing of the motive neurons. And only after the conditioned stimulus was able to turn on these motive neurons did it begin to influence the neurons of the memory grid. This result intimated that the motive neurons might play a role in turning on the hippocampal learning machine.

This was supported by a second finding. When the auditory signal was associated with punishments instead of rewards, the motive set of neurons became inhibited instead of accelerated. And in this case the memory elements failed to acquire any new response at all. This not only corroborated the view that dentate neurons might be required to turn on the hippocampal learning machine but also added to this concept the hypothesis that these neurons represented the promise of *reward* to the hippo-

campus. This was because they were turned on only by reward signals.

The third finding was that, *after training*, the dentate elements (the motive neurons) fired with a *longer* onset time than the memory set. The anatomical arrangement made this a very surprising finding. The dentate neurons projected only to the memory set. The memory set fired first (apparently acknowledging message number one from the conditioned stimulus). And then after firing, the memory set received a second or reconfirming message relayed through the dentate gyrus. Why was the second message needed; what did it add?

One guess was that the dentate activity at this time might represent in a different guise a central anticipatory process related to reward. After training, the message from the conditioned stimulus would be projected to the memory device. There it would trigger a dry run. This would consist in the playback of recordings (like tape recordings) of behavior sequences related to the stimulus. Those previously followed by reward would as a consequence have connections to the dentate gyrus. The replay of these would therefore activate the dentate elements. These would send a second message to the memory grid which would promote the real activation of the correlated behaviors.

This study of learning has not yet pushed through to the solid outcomes I expect of it. It has guided guesses. But when the number of cases studied is still small, this kind of research gives “iffy” data; a very large number of repetitions will be required to ensure that our observations are real findings. The work has nevertheless validated itself to some degree as a way of attacking the higher functions of the mammalian brain.

It has done this by showing the way to solve some problems posed by conditioning. First, what does training do to the input pathway? The data showed that a conditioned stimulus had its access to the brain facilitated; its input channel was oiled and ready. Explorations to explain this pointed to a changed dynamic process in the cortex. Prior to training there was an ongoing barrage in the cortical area of the stimulus. Training silenced this barrage to some degree. We guessed that the barrage was inhibitory—excluding the signal—and its change to a lower rate by training was itself a “dynamic memory process.”

Second, how can we get at other changes that might be ascribed to more permanent growth of new connections? A growth process should take time, and it should not be dependent on continued training. We therefore sought conditioned brain responses that improved not only during training but also during time intervals between training. Experiments were developed in which changes of this kind were easily observed.

**In the end, it is the programs that determine what any computer will do. And it is education that determines what humans will do**

Third, can a small number of recordings from a limited population of neurons get at the intricate workings of machines like the hippocampus. The data showed that the order of changes in the course of learning and the order of firing before and after learning at least helped to organize guesses about these functions.

### Conclusion

Will these studies ever turn a corner and begin to offer a kind of answer that has practical value?

My best hope comes from the fact that they are not totally disconnected. Three sets of practical problems confront a teacher. One is related to interest: to turn on the learning machine and to motivate rehearsals. A second is related to temporary memories: to create processes that cause the trainee to see the appropriate things and to act in appropriate ways. The third is to induce retention: to cause the organization and fixation of long-run memories.

If we can put ourselves in a position to observe the activity of the brain during behavioral processes that are closely analogous, I cannot conceive that this will not sharpen our understanding. I do not believe that the wait for practical consequences needs to be interminable.

My final word is in defense of education itself. It is perhaps surprising that any defense should be needed. But current restatements of our knowledge concerning the genetics of intelligence have been misinterpreted so as to imply that they mitigate the importance of educational and environmental factors. The fact of genetic differences in brain hardware is cited as a reason why the manipulable environmental variables cannot solve our basic social problems. Such logic is absurd. Genetic differences require more, not less, improvement in educational techniques; just as a poorer basic computer would need a better programmer—unless you were planning to junk the poor machine, and it is too expensive for that. In the end, it is the programs that determine what any computer will do. And it is education that determines what humans will do. □



# From Spreading Depression to the Memory Trace

BY ANTHONIE VAN HARREVELD

**One characteristic of animals is the ability to learn from changes in the environment, and to react with changes in behavior**

One characteristic of animals in general, and of man in particular, is the ability to learn from changes in the environment and to react with changes in behavior. This "memory," which is so important for the survival of the individual, is believed by many biologists to be due to more or less permanent changes in the brain itself.

There are several possible mechanisms that could explain such changes. They could be alterations of the chemistry of the brain, with the formation of a specific compound in the brain for each individual memory. Or perhaps the amount of an existing compound involved in the transmission of an impulse from one nerve cell to the next (the synaptic activity) is increased. Another possibility is that brain structures become more sensitive when they are activated by such transmitter compounds. One theory is that structural changes occur in the brain when a memory is established: for instance, new synapses may be formed.

During the last decade we have been making investigations in this laboratory into the unstable nature of the water and electrolyte (salts that can split in charged particles) distribution in the central nervous system. These studies have suggested a possible mechanism underlying the phenomenon of memory. Our research group (consisting Dr. Eva Fifkova, myself, and several research fellows) has been particularly interested in the effect of a specific amino

acid—glutamate—on the water and electrolyte distribution, and how it is involved in the phenomenon of "spreading depression," a condition in which electrical and other activities are temporarily turned off and which spreads at a rate of two to four millimeters a minute in the cerebral cortex. This has recently led us to do research into the role of glutamate in the formation of memory.

In the lower mammals, particularly rabbits and rats, spreading depression especially affects the cerebral cortex, the most complex and highly developed part of the nervous system. When it occurs, all the cortical functions—except metabolic processes and oxygen uptake—are temporarily suspended.

Although glutamate is a natural component of the brain and is present in all the proteins of the body, it can become highly toxic when present in the nervous system in an abnormal distribution. What appears to happen during spreading depression is that glutamate is released from cells and fibers in the cortex into the material between the cells, where it increases the permeability of the membrane surrounding the nerve cells. The increased permeability allows electrolytes and water from the extracellular space to diffuse into the cells and fibers. The electrical potential of the cells is decreased by this effect of glutamate, making it impossible for them to receive or transmit electrical impulses. This explains the loss of function of the cerebral cortex in spreading depression.

Furthermore, this released glutamate causes the nerve cells to release more glutamate, which can then spread and stimulate other nerve cells to release their glutamate. This may be the mechanism by which spreading depression is transmitted through the cortex.

After some minutes the process is reversed, electrolytes and water leave the cells, the membrane permeability returns to normal, the membrane's electrical potential is reestablished, and function is restored. The total blackout persists for five to ten minutes in rabbits.

Wondering what the biological significance of the release of glutamate during spreading depression could be, we

proposed many years ago that spreading depression could be a mechanism to *protect the tissue against overactivity* and overstimulation. We based this idea on the observation in our laboratories that, in the rabbit, convulsive activity triggers spreading depression, which then abolishes all electrical activity for some time. However, since this reaction was not observed in higher mammals (cats and monkeys), we eventually had to assume that protection against overactivity does not seem to be the true function of spreading depression.

These observations, however, led to the conclusion that neural activity causes a release of glutamate, which in the rabbit may then result in spreading depression. This suggested to Dr. Fifkova and me that spreading depression itself may indeed have no real function in the normal operation of the brain and nervous system, but that what we observed as spreading depression may be an abnormal large-scale activity of a mechanism that has its real functional meaning on a microscale.

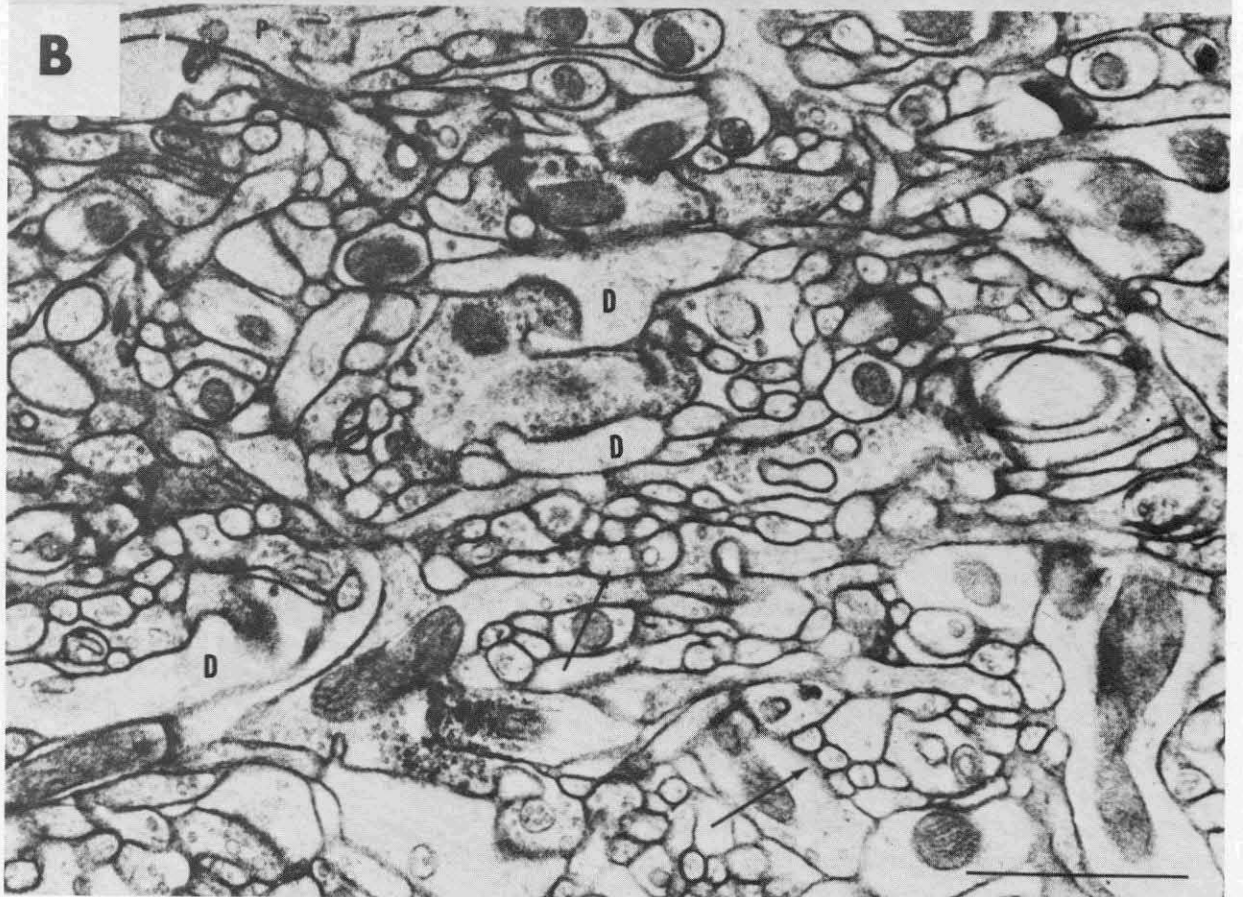
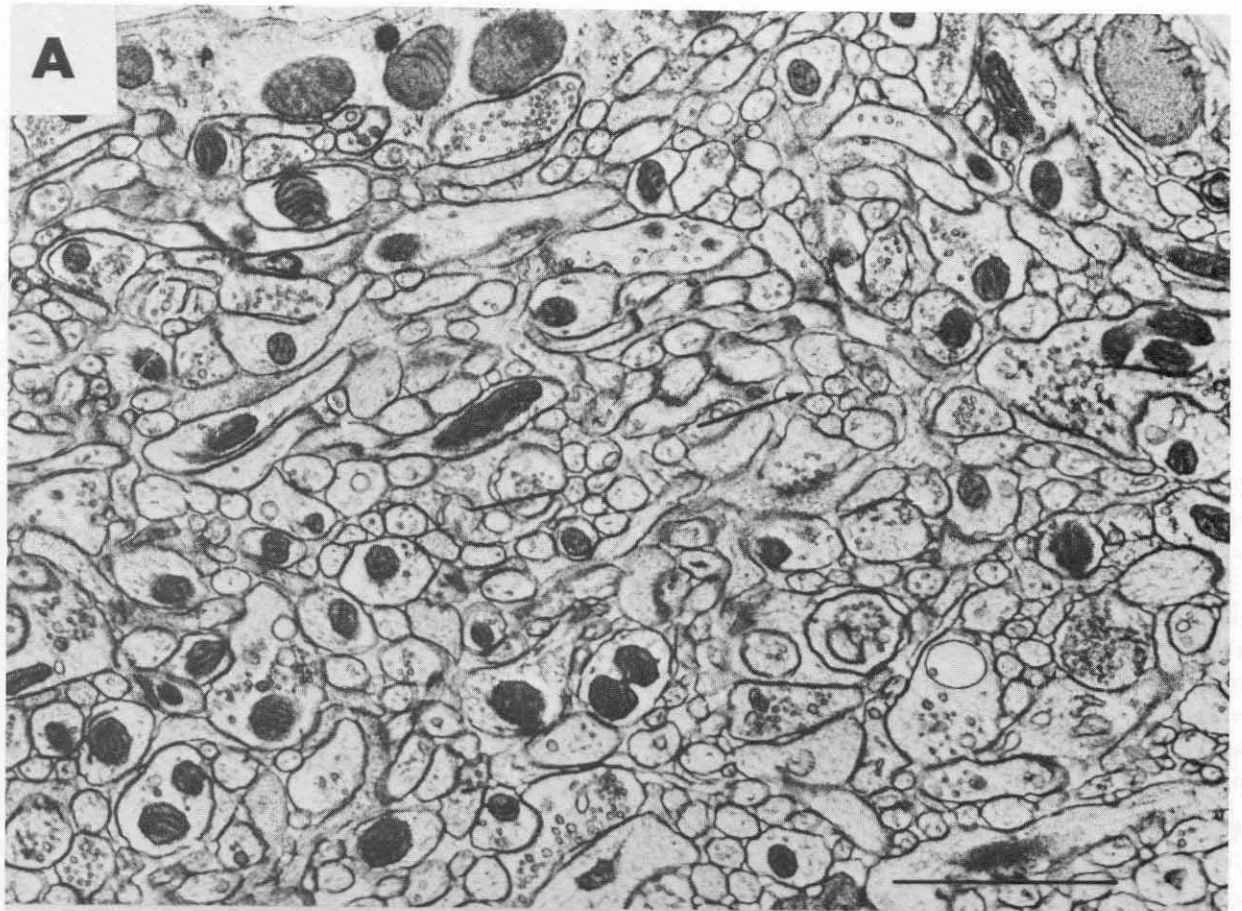
We therefore suggest that glutamate's true role is at the neuronal level, where it may be involved in the mechanisms by which the brain processes information. The activity of the brain could cause a release of glutamate in a pattern determined and shaped by incoming electrical impulses from the sense organs. This would cause localized changes in the configuration of the nerve-cell elements and of the extracellular space, which could change the flow of information in the cortical tissue.

If such a function exists, detecting it would be greatly facilitated by the availability of an antagonist of the glutamate action, because deficiencies in the behavior of an animal caused by administration of such a compound would be a clue to the role played by glutamate in the activities of the brain.

With this in mind, we looked for a compound that could counteract the effect of glutamate. We found that isolated chicken retina (which is really a part of the chicken's brain and can exhibit spreading depression) was a preparation singularly suited to such a search. Using it as a test object,



Anthonie Van Harreveld, professor of physiology, is interested in mammalian physiology, particularly the structural and physiological interactions of neurons in the central nervous system.





we investigated the effects of a large number of amino acids and drugs on the retina's response to stimulation with glutamate. None of the drugs suppressed the glutamate action on the retina, and most of the amino acids did not have any effect. (Some amino acids had an injurious effect, or were undesirable in other ways that prevented their use as glutamate antagonists.)

Only the amino acid, proline, seemed to have features that would make it acceptable as an antagonist to the uptake of extracellular material caused by glutamate. Because it appeared to prevent the structural changes postulated to be involved in the mechanism associated with spreading depression, we decided to examine its effect on animal behavior.

The study of the effects of compounds like proline on the brain function is hampered by the blood-brain barrier which prevents many amino acids and other compounds from passing from the blood into the brain. However, in embryos and in very young animals this barrier is not yet fully developed. From previous experience we knew that in chickens the blood-brain barrier remains permeable for amino acids during the first day after hatching. In such chicks the injection of proline caused no changes in behavior or in brain waves—the most easily noticeable effect of neuronal activity. We therefore looked for less obvious behavioral changes, which led us to investigation of the initial phase in the formation of memory, a function that could well be based on a mechanism involving glutamate. In this early phase, transient neuronal patterns must be transcribed into a more enduring change in the tissue. A release of glutamate patterned by the neuronal activity could well cause such a structural change.

The newly hatched chicken is a favorable subject for such an investigation. These animals tend to peck at small shiny objects, but after they had been offered such a lure moistened with a bad-tasting substance, only a small percentage peck again in later tests. In an experiment in

which chickens were avoidance-trained during proline administration, about 58 percent pecked at the lure when tested 45 minutes later, as compared with 24 percent in control groups that had not been injected with proline. This shows that proline somehow inhibits the formation of the memory trace, perhaps by its effect on the action of glutamate on the neurons.

The path that leads from an initial impulse pattern to a more or less permanent memory is a complicated one, in which several phases have been distinguished that can be affected by different procedures. Such experiments have indicated that memory formation is a multistage affair, spread over a considerable range of time, and probably involving several mechanisms. The extensive literature on this subject suggests that the impulse pattern evoked by the experience to be remembered is first transcribed into a "short-term memory trace" that fades in a few hours, and in turn is replaced by a "long-term memory trace" that may remain for the duration of the animal's life.

The formation of the memory trace can be prevented by an electrically induced convulsion given within 30 seconds after the presentation of the bad-tasting lure. The convulsion may interfere with the electrical activity of the brain which mediates the memory. The long-term memory trace is affected by compounds that inhibit protein synthesis in the brain. There is evidence that proline acts neither on the protein synthesis, nor on the electrical activity, but affects the transformation of the impulse pattern into the short-term memory trace.

This concept of the nature of the short-term memory trace opens the interesting possibility that a structural change in the central nervous system tissue is involved in memory and that this change may be detectable by microscopic examination. It should be kept in mind, however, that the effect of proline on the memory—although suggestive—is no proof that glutamate is involved in memory consolidation. Proline may have effects that interfere with the formation of the memory other than the inhibition of the response of nerve-cell elements to glutamate.

Whatever the mechanism of its action, proline is of interest because it seems to affect a different phase of memory consolidation than that acted upon by electroconvulsive shock or by inhibitors of protein synthesis. Therefore, it supplies a new tool in the search for the explanation of the mystery of memory. □

Opposite: Two photographs taken with an electron microscope show the difference in the amount of extracellular space in the cortex of a mouse brain under normal conditions (A) and during spreading depression (B). The electron density of the various tissue elements is rather uniform. In B the spaces between the small profiles have disappeared, and the plasma membranes look thicker and blacker than in A because they are close together. Certain tissue elements that can be recognized as dendrites (D) are electron transparent and seem swollen. The arrows in both A and B indicate axons, which are nerve fibers that carry impulses away from the neurons.

# The Behavior of Neurons

BY C. A. G. WIERSMA

## Research on the nervous systems of invertebrates is an important link between neurophysiology and behavior

A prerequisite for the development of scientific principles that can lead to an understanding of natural phenomena is the establishment of valid hierarchical levels. In neurobiology, neuronal behavior is one such level. To an as yet unknown extent, knowing how the nerve cells "behave" can bridge the gap between a purely neurophysiological understanding of nerve-cell function and the behavior of the whole animal.

In our laboratory we have used the stimuli and responses of single nerve cells to study the functional relationships of the nervous systems of crustaceans (crabs, crayfish, and lobsters). Among our reasons for using these animals is the fact that their behavioral repertoire is less complex than that of most insects and vertebrates. Compared to clams and snails, on the other hand, their central nervous systems are more in total command, because they have no peripheral neuronal mechanism governing local reactions—except, as in vertebrates, in the circulatory and digestive systems.

Research into the nervous systems of invertebrates like these can materially contribute to our understanding of how central nervous systems in general work, and offers good material to serve as models for studying the complex properties of "higher" functions, like the thought processes in man. It, therefore, provides an important link between neurophysiology and behavior, a subject that should be intensively pursued.

Among the crustaceans, the central nervous system of the crayfish has been best investigated. It has a relatively small number of interneurons (those fibers that connect only with other nerve fibers), and a large percentage of them have been identified and can be recognized in each individual. In addition, these interneurons are large in size, which makes it possible to detect their signals readily

and even to isolate them completely. For many interneurons, it has been possible to study the effects of stimulating them individually.

The sensory interneurons are interesting because their responses indicate which features in the environment the animal selects as important. Motor reflex neurons often illustrate by their patterned output the existence of pre-programmed systems of muscle contractions. And interneurons that are high-level links in complex behavioral reactions are good monitors of the mechanism by which such reactions are obtained. Studying them may be expected to provide important insights for correlating neural and behavioral events. At present it looks as if these concepts are equally applicable to more complex nervous systems—even those of men.

It is clear that the central nervous system in crustaceans deals with incoming information from the sense organs by families of similar interneurons, whose members differ only in their sensory fields. There are a number of such families, each responding to a different type of environmental change. But within these families there are groups of interneurons that react specifically to only one aspect of a particular environmental influence. Optic interneurons, for example, react either to light level or to object motion. The fibers of each family usually have large sensory fields that overlap. This is demonstrated by the fact that one of the family usually covers all of the family's sensory field—for example, for optic interneurons, the whole eye surface—while others respond to only halves, quarters, or other fractions of it. The result is that information generated at any given point is transmitted by a number of interneurons. In other words, parallel computation is widespread in these systems.

Another important finding from our investigations concerns the change in the amount of response shown by many interneurons during different types of activity of the animal—its "moods." Many react more strongly when the animal is active than when it is at rest. For instance, when the so-called sustaining fibers of the crayfish optic nerve are stimulated by light of constant intensity, direction, and duration during rest, they will "fire," sending their messages to the brain in a predictable pattern that varies only somewhat with the amount of light adaptation. But when the animal is in a state of great excitement, as shown, for instance, by its "fight-defense" position,

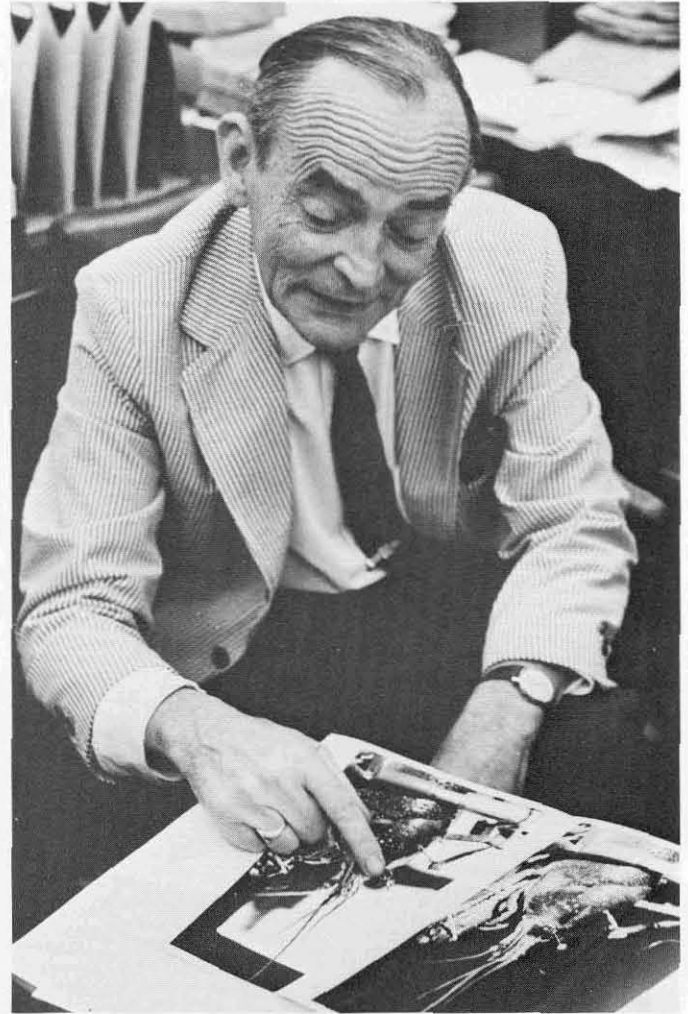
sustaining fibers will fire up to five times more frequently for the same stimulus. If one were not aware of the influence of mood, one would falsely conclude that the light intensity had gone up by a very large factor.

Mood changes also have a considerable effect on the way the output system of the crayfish sends messages to its muscles. Many of the motor neurons to the various muscles, for example, increase their output when the mood of the crayfish changes, and this makes the animal more alert and ready to respond. However, some specific motor fibers are inhibited by the same mood change. For instance, switching to the defensive mood causes the muscles moving the eyecups to contract more strongly—except for the muscles that withdraw the eye, which are inhibited. This makes good sense behaviorally, because when exciting things are happening, one has to see what is going on all around.

Another fiber type of considerable behavioral interest is the space-constant group in the visual system. These fibers always look upward, even when the animal lies on its back, and therefore they represent a kind of gyroscopic system. It is likely that this group of fibers plays a major role in the orientation of the animal with regard to space.

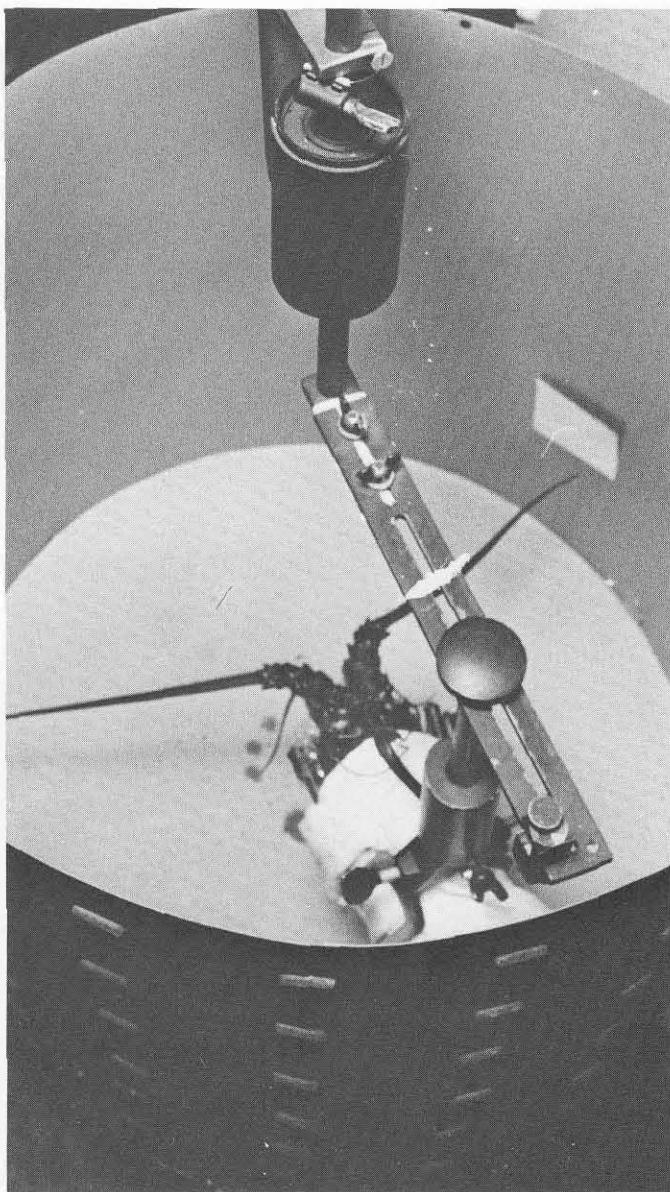
In recent investigations we have focused more on specific “neuronal behaviors” and have tried to link these with the behavior of the animal itself. For example, at least two of the space-constant fibers have an additional function that is directly involved with specific behavioral acts. In the normal body position, the crayfish, when rapidly approached by a large object from above, will often initiate an escape response by flapping its tail. The approach of an object from underneath does not cause this response. But when the animal is lying on its side, an approach within the field of vision of either the ventral or dorsal half of the upward-looking eye will cause a flip of the tail, whereas no response can be obtained from the downward-looking eye. Quite similar observations regarding space constancy can be made for eliciting the defense reflex.

Another promising example that links neuronal activity and animal response is furnished by the family of “seeing” fibers which we have found in the rock (or spiny) lobster. In addition to the more primitive families of visual fibers like those of the crayfish, in the lobster we discovered



C. A. G. Wiersma, professor of biology, has been studying the nervous systems of crustaceans for many years. His most recent research on the functioning of the optic nerve in crayfish may yield important information about the physiology of vision.





Illustrating the link between neuronal activity and animal response, a rock lobster reacts to a white square coming into the visual field by pointing an antenna at it. This crustacean is a relative of the crayfish but has additional, more sophisticated elements in its visual fibers, including seeing fibers, which are very active during this reflex.

truly higher-order elements, whose responses depend on many factors. Usually they react very well when a small target, either black or white, is brought into their excitatory field of vision at a rather slow speed. But they make little or no response to very fast or very slow movement.

The response of these seeing fibers to stationary objects is also interesting. Such non-moving objects are "seen" only by the middle part of the seeing fiber's complexly structured visual field. When an object is placed in front of this part during darkness, lighting it will cause a response, provided the dark period was short. The fiber "remembers" the old situation and compares it with the new; it fires when the object has been added, but not when it has been removed. In order to fire, however, the fiber must "pay attention" and not be distracted (inhibited) by other visual or motor response events.

As an example, in a "forward-looking" seeing fiber, the response, even to a moving target, can be suppressed by presenting another moving object around the edges of the visual field, or by stroking the abdomen or legs. Touching of the head appendages, on the other hand, arouses this fiber's interest even more and enhances its response. Since so many factors are involved in setting the reactivity, or response, level of these fibers, they are rather difficult to study in detail. Using electrodes implanted in the eye stalks, we have made recordings of the neuronal activity when the animal walks around a tank with transparent walls, and we have found that the fibers act the same under these nearly natural conditions as they do when the animal is severely restrained. There are good reasons to believe that this type of fiber (forward-looking seeing) plays an important role in initiating the reflex that causes the rock lobster to point with the tip of its antenna toward an object.

For this pointing reflex we believe that we have obtained one further link in the input-output relationship, in the form of a large interneuron. This fiber passes along incoming information of visual as well as proprioceptive origin and is thus multimodal. The movement of a small object over the eye in one direction causes the fiber to discharge, as does the movement of the antenna in the same direction. It seems likely that this is a command fiber involved in the pointing reaction. Obviously, however, additional pathways must be present to account for the accuracy of the pointing and tracking reactions.

Our previous experiments with the responses of single motor neurons that excite the eye muscles have recently led us to investigate their memory mechanism. We used a formalized version of the marine habitat of the crab in the shape of an upright metal cylinder about 18 inches in diameter and about 20 inches high. The inside of the cylinder's walls is lined with alternating black and white vertical stripes two inches wide. The cylinder can be turned clockwise and counterclockwise.

To monitor the memory responses, two minute metal electrodes are inserted through one of the eye stalks so they contact two specific nerve fibers linked with the memory. One fiber connects the memory mechanism with the muscle that moves the eye to the right; the other links with the muscle that moves the eye to the left. When nerve impulses caused by the memory mechanism stimulate one muscle, the other muscle receives no impulses and thus is deactivated. In this situation, the unstimulated muscle relaxes while the stimulated one contracts and moves the eye. The frequency of the impulses determines the strength of the signal and the amount of eye movement. The frequency ranges from zero to 50 impulses per second. The difference between the frequency of the impulses in the two nerves was used to measure the memory.

In a typical test, the animal is placed in a fixed position inside the cylinder and near its base. It is permitted to view the striped background under artificial light; then the light is turned off. In the darkness the cylinder is turned a short distance. The light is turned on again. The crab can almost invariably tell that the cylinder has been moved, and how much. To do this it must have remembered its prior position. When the background change is made during a five-second dark period, strong responses are obtained. With longer dark periods, the responses become gradually weaker for equal amounts of background displacement, but they are still quite pronounced after eight minutes.

The animals can discern very small angular movements, and with larger background changes, the response strengthens. We conclude that a number of "receiving stations," well distributed over the eye, must be activated to be "interpreted" as motion during darkness. Rotation of the animal gives the same result as background turning, and the former would be the natural stimulus.

Another question we have looked into is how long the

animal must see a given background before it is remembered. In one series of experiments, the striped background at which the animals looked was turned a few degrees in darkness, exposed again for various lengths of time, and then turned back to the original position. The strength of the responses increased as the time increased. In the crab, even a half second is enough to make a difference, but the response grows in strength at least up to 20 seconds—and we always had let the animal look at the control background position for a minute or more to be sure that memory strength was near maximal.

A variation of these experiments showed the kind of struggle that goes on between "old" and "new" memories. Here the background was turned by a given number of degrees, and then—after various exposure times—returned halfway to the original position. With short exposures the old memory is strongest, with longer ones the new memory replaces the old. But at one intermediate time interval, no change in discharge occurs, indicating that the two memories are of equal strength.

We plan to continue this research, hoping to find out such things as how many memory locations are involved and where they are. At present we think there are at least four. The ease with which the system can be handled and the absence of any true learning factor (does a photographic plate learn?) make this system a valuable model for memory study.

In research on the central nervous system there has been a strong tendency to ignore the behavior of the neuron and to emphasize other aspects, but I am convinced that this approach will not be successful in explaining behavior. Investigations of neuronal behavior are likely to provide answers more quickly. One shortcoming in this area that should be rather easy to remedy is the lack of knowledge of the sum total of behavioral acts that a given species can perform. Such information is essential in order for us to be able to correlate the behavior of the neuron with that of the animal. This is true not only for invertebrates, but also for most vertebrates.

The study of the invertebrate nervous systems through the understanding of the neuron is both interesting and intellectually challenging. The field should show impressive growth in the near future and remain a subject for intensive investigation for a long time. □

# A Worm's-Eye View of the Brain

BY RICHARD RUSSELL

Our world is full of complicated machines (computers, for example) composed of very large numbers of fairly simple elements. The nature of these elements to some extent determines how these machines work, but more important is the way in which these elements are connected together. For instance, the same electronic components can be used to make a phonograph amplifier, a television set, or a Moog synthesizer; the difference lies in the way their components are wired together.

The same general principle, of course, applies to our own nervous systems. Our brains are made up of a very large number of nerve cells (probably about ten billion), but the number of cell types is apparently fairly small. What enables different parts of our brains to receive visual stimuli, to integrate these into a picture of the viewed object, and to react to that object with fear or pleasure or arousal is the way in which these cells are connected together.

But what are the principles by which these all-important cellular connections are established, and how do they actually work? The answers to these questions are still largely unknown, primarily because of the extreme complexity of the vertebrate brain. Although considerable progress can be made by asking general questions about the functions of different parts of the brain (see, for example, the articles by James Olds and Roger Sperry on pages 12 and 29), we are still a very long way indeed from a "circuit diagram" of the vertebrate brain.

There is a quite reasonable expectation, however, that some of the principles used in mammalian brain circuit design may also be used in the design of much simpler nervous systems, for which there are reasonable prospects of obtaining a circuit diagram. Several laboratories, ours included, are now studying such simple systems in the hope of revealing some of these principles.

Our organism of choice, the small soil nematode (round-worm) *Caenorhabditis elegans*, was first recognized as virtuous for this purpose by Sydney Brenner of the Medical Research Council Laboratory of Molecular Biology in Cambridge, England. Like other more familiar nematodes (for example, the classical invertebrate-zoology-

course nematode, *Ascaris lumbricoides*, or the trichinosis agent, *Trichinella spiralis*), *C. elegans* has a simple nervous system, with fewer than 300 nerve cells. Unlike these other nematodes it is extremely small—only about one millimeter long—and chooses to live in the soil rather than as a parasite.

Despite the simplicity of its nervous system, *C. elegans* shows a variety of behaviors; it moves with a sinusoidal gliding movement in which its 92 longitudinal muscle cells are exquisitely coordinated; it occasionally reverses, moving backward with equal coordination; it feeds on surrounding bacteria through the pumping action of a muscular pharynx; and when its gut becomes overly full, it defecates by using special muscle cells in its tail. It is attracted to some chemicals, repelled by others, and responds also to mechanical and thermal stimuli. Other behaviors, including a specialized mating behavior, a "social" clumping, and an acrobatic act of balancing on the tail, are exhibited in certain developmental stages or under certain environmental conditions.

One of the interesting general questions which arises in considering *C. elegans* is how such a variety of behaviors can be executed by such a simple nervous system. In order to determine how the component nerve cells are "wired up" to perform these behaviors, we have begun with an anatomical reconstruction in which the small size of *C. elegans* has been a distinct advantage.

Our goal in this reconstruction has been to obtain a complete anatomical analysis of the nervous system including the shapes, branchings, and positions of all the nerve cells, together with their all-important interconnections. We must go about this by using the electron microscope for the simple reason that the interconnections, or synapses, are in general so small that they can only be resolved in adequate detail by the electron microscope. Fortunately *C. elegans* is so small that its whole nervous system can fit in one field of view in this instrument, thereby greatly simplifying the task. Since the electron microscope also requires very thin specimens for its electron beam to penetrate, we must cut our animals up into many thin sections, examine each, and then use all to reconstruct a three-dimensional representation of the nervous system.

Much of our initial effort has gone toward establishing techniques for handling the large number of sections which must be cut and examined for this job. One of these techniques, for instance, is a movie-making process



devised by Randle Ware, a postdoctoral fellow. In this process, thin sections are cut serially (from a fixed and embedded animal), photographed in the electron microscope, and then rephotographed in alignment so that each becomes one frame of a movie film. When projected, this film gives the impression of an "optical trip" through the nervous system, and we use it as a convenient way of determining the detailed shapes of individual nerve cells.

Another technique, just being set up now, uses this sort of movie in connection with a computer graphics display terminal to map the positions of synaptic connections between nerve cells. Individual frames of the movie are projected onto the oscilloscope screen, and a computer-controlled light spot is used to mark and record the positions of synaptic connections. These positions can be

**One of the interesting general questions which arises in considering the worm is how such a variety of behaviors can be executed by such a simple nervous system**

easily retrieved from the computer memory and very efficiently used to determine the patterns of inter-connection among nerve cells. For this phase of our work we are collaborating with Drs. Gilbert McCann and Ken-Ichi Naka of Caltech's information sciences group.

With these techniques in hand or in progress, we have begun our anatomical analysis by concentrating on one



Richard Russell, assistant professor of biology, outlines nerve pathways on a photograph of a cross-section of the small soil nematode. By repeating this process on sections cut serially along the length

of the worm, he can build up a three-dimensional "circuit-diagram" of its nervous system. The diagram on the wall, a work in progress, shows the position of nerve cell bodies in the head of the worm.

## A Worm's-Eye View of the Brain . . . *continued*

part of the nervous system, the sensory part. This is located near the front of the animal, in a relatively confined space, and has proven well suited to anatomical analysis. We have determined the shapes of all of the 68 cells in this part of the nervous system, with particular emphasis on the shapes of the sensory endings by which these cells detect chemical signals, touch, and temperature. Homologies with the structures of sensory endings of known function in other animals have been detected and used to predict the functions of some of the sensory cells. Other cells, to judge by their lack of synaptic contacts, seem to play the role of accessory, non-nervous cells, despite their intimate structural involvement in the sensory endings. A remarkable degree of symmetry has been found, and also a high degree of structural reproducibility from animal to animal, testifying to the tight controls that must be exerted over the formation of this simple system in development.

Recently we have begun to analyze the synaptic contacts of the sensory nerve cells, and already two surprises have confronted us. First, some of the sensory nerve cells make direct synaptic contact with muscle cells which move the animal's head, and we are particularly intrigued to know what role such a simple reflex arc can play in governing behavior. Second, even the central nerve ring, the integrative structure which contains many sensory cell synapses, shows a marked degree of symmetry which will greatly facilitate its eventual structural analysis.

At this point in our structural analysis, some potentially generalizable principles are already emerging; first, in many respects the system appears to be constructed out of simpler cell assemblies, repeated several times and arranged symmetrically in the animal. This principle is very reminiscent of the highly reiterated structures of more complicated nervous systems such as the visual system of dipteran flies like *Drosophila*, or the cerebellum of vertebrates. Second, the degree to which nervous

structure can be reproduced from animal to animal is really quite impressive; not only are nerve-cell bodies almost always in exactly the same positions in different animals, but also the various axons which comprise a nerve bundle are usually in quite characteristic positions within the bundle. Third, it appears that quite simple connections like sensorimotor reflex arcs can be included within much more complicated overall structures.

Our experience so far suggests that as our anatomical analysis continues, more and more principles of this sort will continue to emerge, particularly when we analyze synaptic connections and begin to reveal the structures of some nerve-cell circuits. Initially, of course, the circuits we reveal will simply be anatomically feasible ones, without any evidence that they are actually used in controlling behavior. However, a number of techniques can be used to test the functions of these circuits. For instance, we should be able to eliminate single cells or groups of cells by laser microbeams and thereby determine their functional roles. And there are indications that some neural transmitter compounds may be used by a very small number of nerve cells, whose functions could be selectively eliminated by drugs which block the action of these transmitters.

Perhaps the most comprehensive method, however, involves the use of mutations. Because it is a self-fertilizing hermaphrodite with a very short generation time, *C. elegans* is very well suited for the isolation of genetic mutants. We have already isolated over 300 independent mutants with behavioral alterations, including some which specifically affect the sensory nervous system. Because some of these mutants produce specific and reproducible changes in the structure of the nervous system, they are very useful for testing ideas on how the system functions; if an idea incorrectly predicts the behavioral consequences of a mutational change in nervous structure, then the idea must be scrapped or modified. (Seymour Benzer's article on page 6 discusses other uses of mutations affecting nervous function.)

Once the true functioning circuits of the *C. elegans* nervous system have been revealed by these techniques, the principles of circuit design used in this system should become clear, and it should then be possible to determine whether, as we strongly suspect, these same principles will apply in the construction of more complicated nervous systems like our own. □

# Messages from the Laboratory

BY ROGER SPERRY

**On the present terms, human values become very much a problem for science, and in certain respects perhaps the most important problem today in the whole of science**

When it comes to saying a few words about our research, I am forced to hedge a bit. I am committed to not discuss our neurosurgical patients and their symptoms outside of medical or scientific settings. So I have been asking myself what else there might be of broad general interest. These days we're supposed to ask, "What's relevant?" or, according to the new RANN formula, "What is there in our science that might lead to a prospectus for social change?" Well, I can't speak to this exactly; but I can pick out three facets of our work where the kind of message that we get from the laboratory seems to differ somewhat from that coming from the public media or society at large.

## **Plasticity and Nature vs. Nurture**

The first of these concerns the plasticity of brain organization and human nature. Back when we first began to work in this area, neuroscience was thoroughly sold on a kind of super plasticity in brain function. Among other things, the functional interchangeability of nerves for nerve surgery was taken for granted. Having its wires crossed by the neurosurgeon was no problem at all for the brain back in the 1930's.

When a damaged nerve like that supplying the muscles

of the face had been replaced surgically by a nearby healthy and more expendable nerve—like that for lifting the shoulder, for example—the initial effect was associated movements in the face whenever the subject tried to lift his shoulder. However, the doctrine of the day said that the patient need merely go home and practice in front of a mirror and shortly the plastic brain centers would undergo reeducation to restore normal facial expression, mediated now through the brain centers and nerves designed for shoulder movement.

Efforts were being made to restore function to legs paralyzed by spinal cord lesions by using one of the main nerves of the arm still connected to the brain centers. The arm nerve was dissected out full length, tunneled under the skin, and connected to the leg nerves to take over the function of the paralyzed limb. Only an early report—not the final outcome of this effort—appeared in the literature, perhaps for reasons that are now understandable. However, exactly the same operation was later reported to be a functional success in experimental tests with rats during the 1930's. The motor, the sensory, and even the reflex functions of the paralyzed hind limb were said to have been restored through the transplanted nerves and brain centers of the forelimb.

The nervous system generally appeared in those days to be possessed of a wholesale behavioral plasticity or, as one authority put it, "a colossal adaptation capacity almost without limit." The followers of Pavlov in Russia and of John Watson in this country were speculating (justifiably it seemed) that it should be feasible with appropriate early training and conditioning techniques to shape human nature into most any desirable mold and thus to create a more ideal society.

This kind of thinking was reinforced by various other views of the 1930's; in particular, the prevailing doctrine on nerve growth told us that fiber outgrowth and the formation of nerve connections in the brain during development is essentially diffuse and nonselective. At that time there seemed to be no way by which the nerve circuits for behavior could be grown into a brain directly—that is, prefunctionally through inheritance without shaping by experience. It was supposed that the adjustment of brain connections depended entirely on function and began way back in the earliest movements of the fetus *in utero*—continuing from then on through trial and error, conditioning, learning, and experience.

Last April, Roger W. Sperry, Hixon Professor of Psychobiology, received the 29th annual Passano Foundation Award for achievement in medical science. "Messages from the Laboratory" is adapted from his speech at the dinner on that occasion. A more detailed account of the psychobiology research program may be found in the November 1968 issue of *Engineering and Science*.

Our experimental findings during the 1940's brought, of course, a direct contradiction amounting to a 180-degree about-face on these matters. As we now know, nerves are not at all functionally interchangeable; the brain is not all that plastic; and the growth of nerve paths and nerve connections in the brain is anything but diffuse and nonselective. Neural circuits for behavior are definitely grown in, prefunctionally under genetic control, and with great precision in an enormously complex chemical pre-programmed control system.

It is not just to recall old times that I go back through this history. The point is that the early views that became deeply entrenched all through the 1920's, '30's, and well into the '40's still have not been completely shaken off in areas outside the biomedical sciences. The lingering after-effects of the earlier doctrines may still be found in related disciplines like psychiatry, anthropology, and sociology and also in society at large. In other words, the majority of us still have a tendency to underestimate the genetic and other innate factors in behavior.

This impression comes not only from the earlier work just mentioned, but it continues to be reinforced repeatedly from many different angles. For example, in regard to cerebral dominance and handedness in man, the latest theory, as proposed by Levy and Nagylaki, suggests a two-gene, four-allele model with one gene determining which hemisphere of the developing brain will be language-dominant and a second gene determining whether the preferred hand will be on the same side or opposite the language hemisphere. Counting the recessives and dominants, this gives nine different combinations of inherited gene types or genotypes for handedness and cerebral dominance in man, some of the left-handed types, of course, being much more resistant than others to reversal by training.

Now the left and right hemispheres of the brain are each found to have their own specialized forms of intellect. The left is highly verbal and mathematical, and performs with analytic, symbolic, computer-like, sequential logic. The right, by contrast, is spatial, mute, and performs with a synthetic spatio-perceptual and mechanical kind of information processing not yet simulateable in computers. It is very impressive and compelling in neuro-surgical patients with left and right hemispheres surgically disconnected to see the same person (some claim there are two persons in the one) approach the

same problem, work it, and reach a solution in consistently different ways with quite different strategies, depending on whether the subject is using his left or his right hemisphere.

In other words, these nine genotype combinations, representing different balancing and loadings of these left and right mental factors, provide just in themselves quite a spectrum for inherent individuality in the structure of human intellect. Left-handers as a group have been shown to be different statistically from right-handers in their mental makeup—that is, in their I.Q. and other test profiles. Similarly, males come out differently from females. And females masculinized *in utero* or those lacking one X chromosome come out differently from normal females.

### **The degree of inherent individuality each of us carries around in his brain would probably make those differences seen in facial features or in fingerprint patterns look crude by comparison**

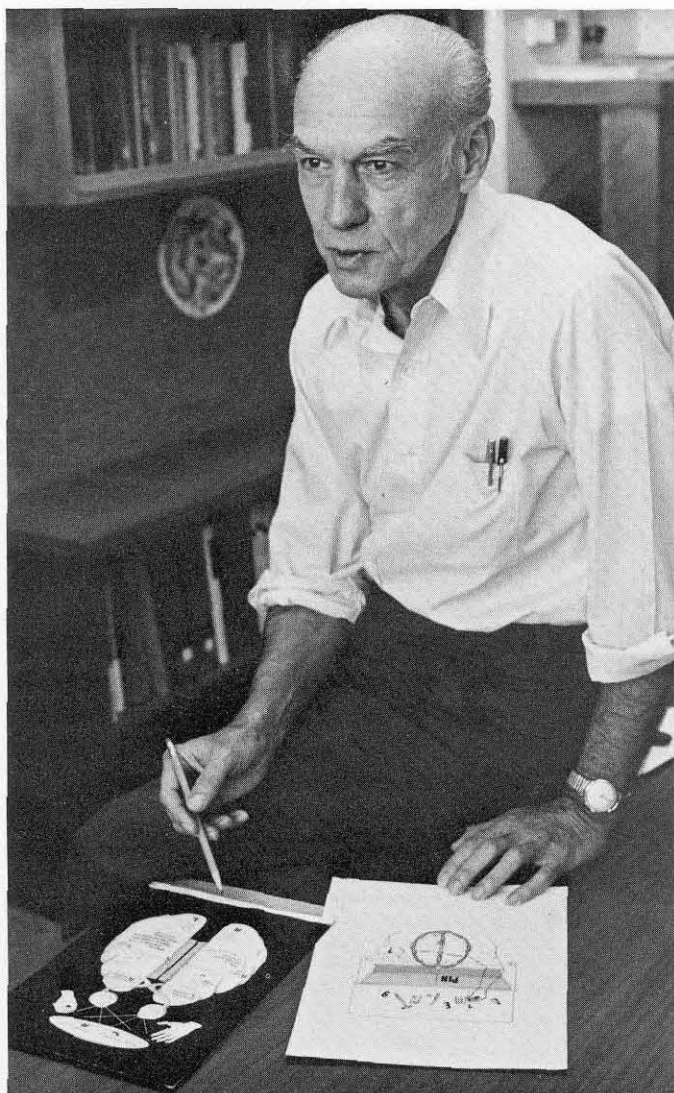
Many kinds of tests have shown that the right hemisphere is particularly talented and superior to the left in visuo-spatial abilities. This specialty of the so-called minor hemisphere, according to a current report by Bock and Kolakowski, is tied to a recessive sex-linked gene and is shown to exhibit a cross-correlation pattern of inheritance from parents to offspring that effectively rules out environment, experience, or any known theory of child development or nurturance.

When we add up all this—and much more—related evidence, we come out with a greatly heightened respect and appreciation for innate individuality. The degree and kind of inherent individuality each of us carries around in his brain—in its surface features, its internal fiber organization, microstructure, chemistry—would probably make those differences seen in facial features or in fingerprint patterns look crude and pale by comparison.

### **The Neglected Minor Hemisphere**

We turn now to a second message that emerges from the





Roger Sperry, Hixon Professor of Psychobiology. His research strongly suggests that our present educational system—with its heavy emphasis on early training in the three R's—discriminates against the brain's minor hemisphere, which has its own perceptual, mechanical, and spatial mode of apprehension and reasoning.

findings on hemispheric specialization and which tells us that our educational system and modern society generally (with its very heavy emphasis on communication and on early training in the three R's) discriminates against one whole half of the brain. I refer, of course, to the nonverbal, nonmathematical, minor hemisphere, which we find has its own perceptual, mechanical, and spatial mode of apprehension and reasoning. In our present school system, the minor hemisphere of the brain gets only the barest minimum of formal training, essentially nothing compared to the things that we do to train the left, or major, hemisphere. (As a curious aside here, statistics indicate that athletic abilities correlate with enhancement of visuo-spatial mental ability. It follows as an interesting conjecture that advancement in our understanding of the cerebral substrates of intellect could make for a slight comeback in the old prestigious image of the "strong, silent man" of pioneer times—an image that is much submerged, of course, in our present-day verbal society.)

### Behaviorism in Question

A third and final message for social change that we get from the world of the laboratory is a complex one and cannot be summarized simply.

One of the more important things to come out of our brain research in recent years—from my own standpoint, at least—is a modified concept of the nature of the conscious mind and its relation to brain mechanism. The new interpretation, or reformulation, involves a direct break with long-established materialistic and behavioristic thinking that has dominated neuroscience for many decades. Instead of renouncing or ignoring consciousness, the new interpretation gives full recognition to inner conscious awareness as an important high-level directive force or property in the brain mechanism. The conscious mind no longer is set aside as a passive correlate, but becomes instead an essential part of the brain process endowed with causal potency. The phenomena of inner experience are conceived to be "emergent" properties of brain activity and become causal determinants in brain function.

On these new terms consciousness is given a use, a reason for being, and for having been evolved in a material world. Not only does the brain's neuro-physiology determine the mental effects, as has generally been agreed, but now in addition the emergent mental operations are conceived in turn to control the component

## Messages from the Laboratory . . . *continued*

neurophysiology through their higher organizational properties and the universal principle of the power of the whole over its parts.

This revised interpretation, since its appearance about ten years ago, has gained considerable acceptance and support. After more than 50 years of strict avoidance on Behaviorist principles, in the last 5 years, terms such as “mental imagery” and visual, verbal, auditory “images,” and the like have exploded into wide usage as explanatory constructs in the literature on cognition, perception, and other higher functions.

The revised interpretation brings the conscious mind into the causal sequence in human decision-making—and therefore into behavior generally—and thus back into the realm of experimental science from which it has long been excluded. This swing in psychology and neuroscience away from hard-core materialism and reductionism back toward a new, more acceptable brand of mentalism tends now to restore to the scientific image of human nature some of the dignity, freedom, and other humanistic attributes of which it has long been deprived by the behavioristic approach.

Old metaphysical dualisms and the seemingly irreconcilable paradoxes that formerly prevailed between the realities of inner experience on the one hand and those of experimental brain science on the other become reconciled today in a single comprehensive and unifying view of mind, brain, and man in nature. Within the brain, we pass conceptually in a single continuum from the brain’s subnuclear particles on up (through atoms and molecules to cells and nerve circuit systems without consciousness) to cerebral processes with consciousness.

These changing concepts of mind substantially alter the general image of man and his role as drawn in the Behaviorist tradition, and also bring other major departures from traditional materialist doctrine.

When subjective values are conceived to have objective consequences in the brain, they no longer need be set off in a realm outside the domain of science. The old adage that science deals with facts, not with values, and that value judgments lie outside the realm of science no longer applies in the new framework.

Instead of separating science from values, the present interpretation (when all the various ramifications and logical implications are followed through) leads to a

stand in which science becomes the best source, method, and authority for determining ultimate value and those ultimate ethical axioms and guideline beliefs to live and govern by. By science here, I refer broadly to the knowledge, understanding, insight, and perspectives that come from science. But more particularly I am thinking of the principles for validity and reliability and credibility of the scientific way as an approach to truth—insofar as the human brain can comprehend it. In other words what has been called “Scientism” gets a new boost now, with added dimensions and a whole new look.

On the present terms human values become very much a problem for science, and in certain respects perhaps the most important problem today in the whole of science. Viewed objectively, human value priorities stand out as the most strategically powerful causal agent now shaping events on the surface of the globe. More than any other causal system with which science now concerns itself, the human value factor is going to determine the future.

I tend to rate the problem of human values Number One for science in the 1970’s, above the more concrete crisis problems like poverty, population, energy, or pollution on the following grounds: First, all these crisis conditions are man-made and very largely products of human values. Further, they are not correctable on any long-term basis without first changing the underlying human value priorities involved. And finally, the more strategic way to remedy these conditions is to go after the social value priorities directly in advance, rather than waiting for the value changes to be forced by changing conditions. Otherwise we are doomed from here on to live always on the margins of intolerability, for it is not until things get rather intolerable that the voting majority gets around to changing its established values. It is apparent, further, that other approaches to our crisis problems already receive plenty of attention. It is the human value factor that has been selectively neglected and even considered, on principle, to be “off limits” to science.

The upshot of all this would in effect promote science into a higher social role above that of the provision of better things for better living—or the prediction, control, and understanding of natural phenomena. Science on these terms becomes a source and arbiter of values and belief systems at the highest level—man’s best channel for gaining an intimate understanding of and rapport with those forces that control the universe and created man. □

# Line Detectors, Lion Detectors, and the Critical Period

BY JOHN PETTIGREW


**Some studies of the remarkable nature of the changes that can be wrought on the developing brain by environment**

The five hundred million or so neurons in the visual cortex of a mammal permit him to estimate the statistical properties of the outside world. Each neuron has a specific "trigger feature" that will cause it to fire when this feature is present in the outside visual space. Such a feature will produce a certain sequential pattern of activation of the receptors in the eye; these ultimately send the information they received on to the cortex to activate the vision.

This discovery was made by David H. Hubel and Torsten N. Wiesel at the Harvard Medical School in the early 1960's when they discarded the use of high-intensity flashes of light and studied the response of single nerve cells in the visual cortex by projecting various patterns on a screen in front of a cat. They found that the trigger feature of the single cortical neuron was highly specific; the neuron would respond only if there was a contour or edge with a specific orientation in a specific part of the visual field. In addition, the line usually had to be moving, often in a specific direction at a specific velocity. Different neurons had different preferred orientations so that in a normal cortex there were cells that covered the full range of orientation around the clock.

Trigger features of cortical neurons can take a great variety of forms, and in the primary visual cortex at least five different stimulus dimensions are represented at each point in the visual field:

1. ORIENTATION.
2. BINOCULARITY. Every cell gets a separate input from each eye. This has two aspects: ocular dominance—there being some variation in the strength of activation from the two eyes; and disparity—there being variation in the precise positions of the two retinal areas, one in each retina, that activate the cells. (This variation in retinal disparity provides a cue to the distance of the trigger feature.)
3. CONTRAST. Some cells respond only if the stimulus is black on white, others respond if it is white on black;



John Pettigrew, assistant professor of biology, is investigating the importance of early experience in the development of visual perception in animals. The work has important applications to the study of visual problems in human beings and how these affect learning.

some cells respond to an advancing dark edge, a receding light edge, and so on.

4. **SPEED AND DIRECTION OF MOVEMENT.** Many cells respond only when the required contour is moving, and for some cells, the movement must be sharply defined for both speed and direction.

5. **SIZE.** Some cells respond only to targets whose size does not exceed some optimal value.

### **Modifiability of the Trigger Feature**

The discovery that single neurons have surprisingly specific trigger features has been succeeded by the discovery that the specific trigger features are dependent upon early visual experience. In the case of kittens, this means about two or three months after birth. During this time, when interconnections between cortical neurons are being formed and reformed at a rapid rate, subtle changes in stimulation cause long-lasting changes in organization; hence the term "critical period" in cortical development.

In the initial experiments it was shown that the second aspect of the trigger feature, binocularity, could be profoundly altered by closing one eye of a kitten during this critical period of cortical development. After such eye closure, neurons are preferentially activated by the eye that was open during early postnatal development.

A second vivid demonstration of the effect of early visual experience on specific cortical neuron properties was provided by H. V. B. Hirsch of the State University of New York at Albany. He raised kittens in total darkness except for a short time each day when they wore masks that restricted what they saw to contours of a specific orientation. Afterward, the kittens were found to have cortical neurons that responded preferentially to orientations present during the rearing; no neurons could be found that responded selectively to orientations the kittens had not seen.

Further confirmation of the plasticity of the orientation detection aspect of cortical neurons came from Colin Blakemore of Cambridge University, who raised kittens in long cylinders painted with stripes of different orientations. Afterward, the kittens had a striking deficit—both behavioral and physiological. This deficiency becomes obvious when two kittens—one raised in a vertical environment, with vertical stripes, and the other raised only with horizontal stripes—are put into a normal room for the first time. It is clear that they have visual capabilities,

but when one tries to get them to play with a stick in their usual kittenish way, they will do so only one at a time. If you hold the stick vertically and move it, one kitten will come forward, follow it, and play with it, while the other looks about vacantly. The roles are reversed when you hold the stick horizontally. When they were examined physiologically with microelectrodes, both kittens had a striking absence of neurons that would respond selectively to the orientation the kitten had not seen during development. In other words, the kitten raised in the vertical-striped environment had an unusual number of neurons that responded selectively to vertical contours, but none that responded selectively to horizontal contours.

## **The discovery that single neurons have specific trigger features has been succeeded by the discovery that these features depend on early visual experience**

A recent experiment underlines the remarkable nature of the changes that can be wrought on the developing brain by the environment. If a kitten is raised so that it never sees lines at all, then subsequently no neurons can be found that respond selectively to lines—whatever their orientation. This was discovered when we reared kittens in a planetarium-like environment—a big black sphere with little holes drilled in its roof so that the kittens' visual experience was confined to small pinpoint sources of light. When we examined the visual cortex of these kittens, we found a large number of cells with very unusual properties. Normally, in the visual cortex each cell has a specific requirement for a line or edge at a particular orientation. But in these kittens we found many cells that could be activated from a large part of the visual field by a tiny light spot. If the size of the spot was increased beyond about half a degree, the cell failed to respond. In a large sample of cells we could not find any that gave the usual vigorous and highly selective responses to elongated line stimuli

### **Implications for Humans**

The finding that the specific orientation of single neurons to lines of that particular orientation is dependent upon the presence of contours of such orientation in the early visual environment led directly to the understanding of an effect in humans with astigmatism. This effect, called meridional amblyopia (partial blindness for orientations across a particular meridian) had been puzzling.

If a normal subject is tested for his ability to discern the lines in a grating of black and white stripes as a function of its orientation, he is able to see a much finer horizontal or vertical grating than one that is oblique. When the subject has ocular astigmatism (so that the lens of his eye



is more powerful in one axis than another), the retinal image is blurred along one axis. However, even with perfect optical correction of the astigmatism, it is found that this subject will still have a deficiency in his ability to discern the lines of a grating whose orientation corresponds to the one that was blurred in his early life, before he was prescribed spectacles. Thus, even though there is now a sharp image on the subject's retina, the subject is still much poorer, because of a defect in the neural circuitry, at discriminating oriented lines having the same orientation as that blurred in his early childhood. Recent work suggests that if this optical abnormality is recognized and corrected early in childhood, the neural defect can be prevented.

One may even ask whether the normal subject's ability to discern horizontal and vertical contours more easily than oblique ones may not be the environmental result of the predominance of horizontal and vertical contours in Western architecture. A preliminary study on Cree Indians, who live within the sloping walls of wickiups, has failed to show a visual preference for horizontal and vertical over oblique, suggesting that Western architecture has in fact a mind-bending effect.

#### Nature and Nurture

While I have laid much stress on the plastic and modifiable properties of cortical neurons, let me also stress their limitations. First of all, a young kitten with *no* previous visual experience does have neurons with slight preferences for specific visual stimuli. These vague, initial preferences probably determine to some extent the direction of the shaping induced by environmental influences. For example, most visual neurons in a totally naive kitten have a specific sensitivity for movement, often in a specific direction. This movement sensitivity persists in an environment that is *stroboscopically* illuminated and therefore devoid of the stimulus of image motion.

Secondly, there appear to be marked individual variations in responses developed to visual stimulation during the critical growth period of kittens. In a number of cases I have observed quite different outcomes from identical visual stimulation in two kittens of comparable age. This becomes particularly striking in those cases where visual stimulation is potentially ambiguous or rivalrous and where the animal might have to make some choice about which aspect of the stimulus is important. For example, if one orientation is presented to one eye, and a different orientation is presented simultaneously to the other eye, it is possible to get two quite distinct types of resultant cortical organization in different kittens. In one type the cortex appears to be organized about the *particular eye* (ocular dominance) so that those neurons are grouped together which are driven only by one eye and only by the orientation to which that eye was exposed.

In the second type the cortical organization appears to be based primarily on orientation; one finds groups of neurons that respond to a particular orientation, but which may be driven by either—or both—of the eyes. This is surprising because it indicates that many cells are driven only by one eye, but by an orientation different from the one which that eye saw *during the rearing*.

In addition there appear to be marked species differences. The phenomena I have described for the kitten may not apply to the rabbit—a prototypical prey animal that does much information processing (including the processing for orientation) in its eye, which sends this information directly to the brainstem for action. In the cat, most of the neurons with *highly specific trigger features* are found in the visual cortex, which provides the most important input to the brainstem, where action patterns can be triggered. In contrast, the rabbit has large numbers of neurons with highly specific trigger features in the eye itself. These cells project directly to the brainstem, which is therefore much less dependent upon information relayed to it via the cortex. In the rabbit, then, one finds that rearing in an environment with a specific orientation has no effect on the development of the distribution of preferred orientations in the cortex, presumably because information about that orientation has been transmitted from the retina, where the connections were permanently established before visual experience.

Perhaps evolution provided an opportunity for a carnivorous animal to be partially freed from innate prewiring because of the long periods of dependence and protection afforded by parents. The need for a built-in "lion detector" is clearly not so great for the lion cub, protected as he is for so many months within the pride, as it is for the young zebra foal born on the veldt, who must be equipped for flight very soon after emerging from the uterus. Following this analogy, one would expect that environmental influences on cortical development will be of supreme importance in the most altricial (the most helpless at birth, that is) of all animals, the primate.

Perhaps the greatest hope for education lies in the possible definition of the time of onset, time course, and exact sequence of the critical periods for the development of "higher" cortical analytical processes, like those used for verbal, visual, and musical communication. Is it possible that everyone could have perfect pitch if we knew the precise time at which to expose the developing brain to the chromatic scale? □

## In This Issue . . . . .continued

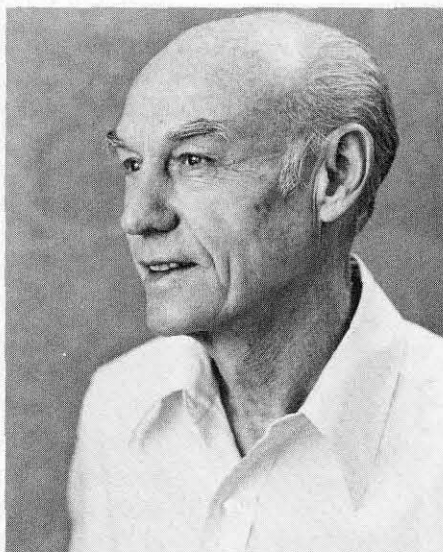
### Richard Russell

Richard Russell, assistant professor of biology, graduated from Harvard in 1962 and then came to Caltech to do graduate work in phage genetics, with a minor in chemistry. His PhD was granted in 1967, and he spent the next year as assistant professor of biology at Cornell University. For three years after that he was a post-doctoral fellow at the Medical Research Council Laboratory of Molecular Biology at Cambridge University in England. He worked there first on the study of transfer RNA and then began his research into the genetic blueprint of the nervous system in the nematode. Still working on the nematode, he is now trying to learn more about the molecular composition of synapses and how genes control their formation.

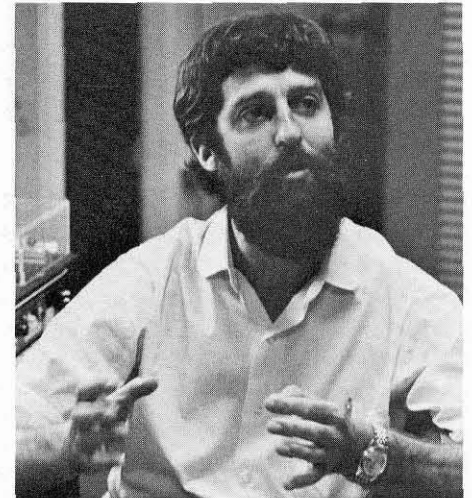


### Roger Sperry

Roger Sperry, Hixon Professor of Psychology, attended Oberlin College, majored in English literature, and received an AB in 1935. Influenced by his undergraduate courses in psychology, he switched to that field for graduate study, earning an MA at Oberlin and, in 1941, a PhD in neurobiology from the University of Chicago. He joined the Caltech faculty in 1954, after a distinguished career at the Yerkes Laboratory of Primate Biology, the University of Chicago, and the National Institutes of Health—plus service during World War II on a government research project on surgical repair of nerve injuries. In 1971, the American Psychological Association gave him its Distinguished Scientific Contribution Award, citing him for "his now classic studies of sensory and motor integration, and his bold and original work with the split-brain preparation, both simian and human. His early work is still definitive with respect to the restoration of motor control following nerve injury in mammals. It is not too much to say that his recent studies of patients with section of the corpus callosum are epochal. . . . These are fundamental contributions to our knowledge of the nature of man."



### John Pettigrew



John Pettigrew, who was recently appointed assistant professor of biology, comes to Caltech this month from Australia—by way of a three-year postdoctoral stint at UC Berkeley. His research has been concerned with how mammals perceive their environment and the importance of early experience in the development of this perception. He is the co-discoverer of a class of "binocular" nerve cells in the cat which measures depth by the amount of difference in the fields of vision of each eye. Pettigrew was born in Wagga Wagga, New South Wales, and received his BS, MS, and MD from the University of Sydney.

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# Manufacturing.

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a few engineers. So we thought a series of ads explaining the work they do might come in handy. After all, it's better to understand the various job functions before a job interview than waste your interview time trying to learn about them.

Basically, engineering at GE (and many other companies) can be divided into three areas. Developing and designing products and sys-

tems. Manufacturing products. Selling and servicing products.

This ad outlines the major types of work found in the Manufacturing area at GE. Other ads in this series will cover the two remaining areas.

We also have a handy guide that explains all three areas. For a free copy, just write: General Electric, Dept. AK-2, 570 Lexington Ave., New York, N.Y. 10022.

### Manufacturing Engineering

Manufacturing engineers plan and specify exactly how a product will be manufactured. They consult with design engineers to make sure a product design is producible efficiently and at competitive cost. They develop, design, provide and maintain the machinery, tools, processes and equipment needed to manufacture a product. And they plan and detail all the interrelated work procedures to be followed during each step of manufacturing. Requires intimate familiarity with all aspects of the production facility, including automation programs.

### Factory Management

Factory managers supervise a factory's work force, materials and machines. Their job is to meet production schedules while maintaining product-quality standards, plant efficiency and a favorable working environment. To do this, they consult with, and implement the plans of, manufacturing engineers, quality-control engineers and materials experts. They also deal directly with the factory's production workers on a regular basis. Thus, good interpersonal skills and the ability to manage large numbers of people are vital.

### Quality Control Engineering

Quality control involves four kinds of specialists. The Quality Assistance Engineer works

with marketing, engineering and manufacturing to coordinate the overall design and maintenance of all quality-related activities. The Quality Control Engineer takes quality standards established for a product by the marketing people, then plans and specifies all test requirements, inspections, audits and personnel needed to meet these standards. He also works with manufacturing to make sure production facilities are adequate to meet quality standards. The Process Control Engineer is responsible for implementing the plans of the Quality Control Engineer.

And for providing technical help to manufacturing to resolve quality problems. The Quality Information Equipment Engineer either designs or purchases, then plans the maintenance of the quality-testing equipment.

### Materials Management

Engineers in Materials Management plan and control the flow of materials throughout the business cycle. They make sure all raw materials, parts, subassemblies and finished products are at the right place, at the right cost, at the right time. This involves scheduling factory production, planning and forecasting material requirements, and determining inventory levels. Also purchasing materials, directing material flow during manufacturing, and warehousing and shipping finished products. Requires knowledge of products, processes and ability in areas such as logistics, mathematics and computer applications.

