Genes and Behavior

By SEYMOUR BENZER

Genes (DNA) that influence structure, genes that influence chemistry —and now we look for genes that influence behavior. Drosophila flies again!

Much of human personality is determined by heredity. For instance, recent studies have revealed that inmates of institutions for the criminally insane show an unusually high frequency of chromosomal abnormalities—suggesting that undue emphasis might have been placed on environmental factors in causing their behavior. To understand what lies between the gene and the personality is a great challenge for modern biology.

Since humans, especially the criminally insane, are not the most cooperative of subjects, one looks for a more amenable creature as a model system. Research has shown that the basic principles of genetics and molecular biology, whether for bacteriophage or the fly, have wide applicability to other organisms. The same may be true for the mechanisms underlying the wiring-up and functioning of the nervous system. The genes contain the information for the circuit diagram, but little is known about the relationship between this primary information and its conversion into the end result. During development, tags of specificity are parceled out among the neurons so that they connect in the proper network. How this is done is an open mystery. It is not even known what kinds of molecules carry the specificity that distinguishes one neuron from another. How does a neuron know where to go and how to recognize others so that only the appropriate connections are made?

Once assembled, the functioning nervous system embodies a complex of interacting electrical and biochemical events to generate behavior. The fine structure and interlacing of even the simplest nervous systems are such that to dissect them requires a very fine scalpel indeed. Gene mutation can provide such a microsurgical tool; with it one might hope to analyze the system in a manner analogous to the one which has proven so successful in unraveling biochemical pathways and control mechanisms at the molecular level.

The wealth of genetic knowledge of the fruit fly, *Drosophila,* and the availability of many mutants and special chromosomal arrangements make it an organism of choice for the genetic approach. The same features that favored *Drosophila* for genetics; namely its short generation time and the facility with which large populations can be grown in the laboratory, also make it advantageous to use for behavioral tests—which can be applied to populations rather than to individuals—and for the isolation of rare mutants by selective techniques.

There are two objections to choosing *Drosophila* for such studies. The first is that it is too big: Its brain contains around one million neurons, a rather complex system. The second is that it is too small: Many of the usual techniques of neurophysiology are not applicable with ease. In some ways, however, I feel (like Goldilocks) that it is just right. The number of neurons, being close to the geometric mean of a single neuron and the human brain, is sufficient to display many of the aspects of behavior associated with higher organisms. On the other hand, it is possible to focus one's interest upon a smaller, simpler part of the system. For instance, the compound eye of the fly consists of about 800 ommatidia in a neat hexagonal array, each containing eight photoreceptor cells. The axons of these photoreceptor cells are distributed to a hexagonal lattice of interneurons in the first optic ganglion in a precise pattern that is reducible to repeated identical subunits, the morphological unit containing only eight photoreceptor axons and one interneuron. Thus, what at first glance appears to be a formidably complex structure can be reduced to a relatively simple system for studying neurospecificity.

Most of the behavioral work with *Drosophila* in the past has been concerned with mating behavior because of its importance in evolution (and partly, perhaps, for secret reasons of the investigators). Flies do, in fact, engage in an elaborate courtship ritual that can be embarrassingly anthropomorphic. Intriguing as these experiments may be, they suffer from a serious drawback; namely, that it takes two to tango. One therefore must reckon with the interaction of the behavioral idiosyncrasies of both the male and the female. Things are bad enough with only one fly.

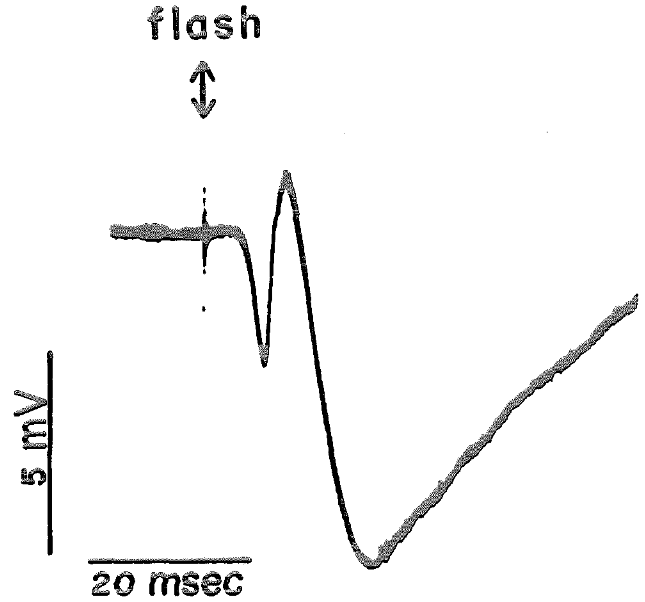
Take the response of a fly to light. To observe this, simply lift the lid of a garbage can. Activated by vibration, the fly moves in the direction of the light, thereby escaping. This behavioral reaction, phototaxis, obviously has positive survival value for the fly. Although relatively simple as behavioral phenomena go, it is nevertheless the result of a complex series of events in an intricate structure. There is absorption of light by photopigment to produce neural excitation, transmission at synaptic junctions, integration in the central nervous system with other inputs, and generation of appropriate motor signals to activate the muscles so that the fly moves in the correct direction.

This system contains models of many of the basic neural mechanisms involved in all behavior. A defect in any one of the structures or processes involved can lead to modification or elimination of the response. Thus, there are mutants known that do not show any response to light. Among a collection of such non-phototactic mutants, one might expect to find defects affecting the various elements of the system.

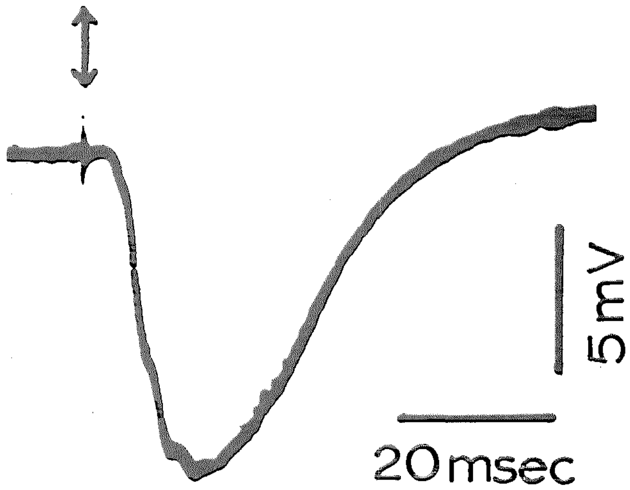
To find these defects, one treats normal flies with a mutagenic agent and isolates mutants that do not show the normal phototactic response. Additional material is provided by the vast collection of previously isolated *Drosophila* mutants available at Caltech, some of which are non-phototactic. To localize the defect, the first step is, of course, anatomical examination of the fly (below). Some mutants simply have no eyes, so the lack of response is easily enough explained. It is interesting to note, however, that such eyeless flies are, in other respects, quite normal, active, and fertile. This points up an important feature of the visual system as a choice for these genetic studies: It is dispensable. Genetic defects—large or small—provided their effects are localized to the visual system, can be picked up without interfering with viability.

Other non-phototactic mutants can be seen to have defects such as absence of photoreceptor cells, gross distortion of the ommatidial array, or degeneration of the neural elements behind the eye. Still, there is also a class of mutants whose eyes appear normal by microscopic examination, yet the flies show no phototaxis. Yoshihi Hotta of Caltech has begun to examine these by neurophysiological techniques. Even by the most elementary method, the electroretinogram, it can be shown that some of

A horizontal section, 10 microns thick, through the eye of a normal Drosophila *is stained with silver to show the nerve fibers. At left are the photosensitive elements of the eye that connect with the various optic ganglia.*



An electroretinogram (ERG) of a fly records the nature of its response to light (phototaxis). The ERG above shows the potential of the cornea versus time in a normal fly after a 20-microsecond flash of light.



ERG of a non-phototactic fly with a genetic defect in the retinal function. The main negative move of the ERG shows that the photoreceptor cells are functioning properly. But in this mutant, the flash of light fails to induce the normal neural impulses indicated by the sharp positive peak in the ERG of the phototactic fly at left.

these mutants have defects in eye function (above). Thus, the photoreceptor elements appear to be functioning properly, yet the neural impulses normally generated in response to photoreceptor action are not produced. Whether this is due to a genetic alteration of excitability of the photoreceptor cell axon or due to failure to transmit excitation to the next interneuron has not yet been determined. An interesting feature of these mutants is that they also show changes in body pigmentation, which may be an important clue to an underlying biochemical mechanism. Finally, there remain mutants that have perfectly normal electroretinograms yet are not phototactic. Their defects must be sought at higher levels of the nervous system.

This search for defects in non-phototactic mutants describes the outline of a research program to attack the mechanisms underlying behavior by genetic methods. It is by no means limited to phototaxis, which is simply one model system. The problems of development of the nervous system, rhythms in behavior, and learning may yield to the same approach. The vast majority of work in neurophysiology in the past has been done with organisms that are impractical for genetics. These organisms may have inordinately long generation times, require difficult conditions for growth and breeding, or both. Conversely, geneticists, with only a few exceptions, have concerned themselves rather little with behavior, preferring to use easily identifiable morphological or biochemical characters as indicators for their genes. To join these two widely separated areas calls for a non-disciplinary outlook.

Actually, there is already a movement among molecular biologists to tackle behavior in various organisms. For example, Julius Adler of the University of Wisconsin is studying chemotaxis in bacteria. Max Delbrück of Caltech is working on phototropism in a mold, Sydney Brenner of Cambridge University has taken up the nervous system of the nematode, and Francois Jacob of the Pasteur Institute has now plunged in with the same animal.

Each of these organisms is, like *Drosophila*, too big and too small but offers certain advantages. The common denominator in all cases, however, is genetics, since molecular biologists are, from past experience, keenly aware of the importance of the genes in determining the development and structure of an organism and of the power of mutations as a dissecting tool. It is of interest to note that many of these people had already switched their fields once before—to go into molecular biology when it was a pioneering venture. But the rapid development of that field has made it, within two decades, a classical science. Whether these renegades can repeat their performance on new and more difficult problems remains to be seen. □