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From the Gene to Behavior

Seymour Benzer, PhD

The problem of gene structure and coding was exciting while it lasted. The story of the past two eventful decades, including my own contributions, has been well told,[1-3] and need not be repeated here. But molecular genetics, pursued to ever lower levels of organization, inevitably does away with itself: the gap between genetics and biochemistry disappears. More recently, a number of molecular biologists have turned their sights in the opposite direction, ie, up to higher integrative levels, to explore the relatively distant horizons of development, the nervous system, and behavior. When the individual develops from an egg, the one-dimensional information contained in the linear sequence of genes on the chromosomes is somehow translated into a two-dimensional blastula, which later folds to produce a precise three-dimensional array of sense organs, central nervous system, and muscles. Finally, the ensemble interacts to produce behavior, a phenomenon which requires four dimensions, at the least, to describe. The genes contain the information for the circuit diagram, but little is known about the relationship between this primary information and the end result. How the tags of specificity are parceled out among the neurons so that they form the proper network, or even what kinds of molecules carry the specificity are, at present, complete mysteries. The problem of tracing the emergence of multidimensional behavior from the genes is a challenge that may not become obsolete so soon.

It is well established that the genes speak strongly in determining anatomical and biochemical features. It should not be surprising if, to a large degree, the genes also determine behavioral temperament, although, of course, environmental influences can also play a large role. All behavior is inevitably the resultant of both components.[4] To discern the genetic contribution clearly, the thing to do is to keep the environment constant and change the genes. This is not easy to do with human beings; they are notoriously uncooperative and unwieldy experimental subjects, particularly if one must wait generations for the results. For this reason, the molecular biologists who have turned to studying behavior have cast around for more favorable model organisms. There immediately arises the problem that the simpler an organism is, the less likely it is to exhibit behavioral patterns that are relevant to man, while the more complex it is, the more difficult it may be to analyze. A wide range of organisms is under attack by genetic methods, including *Escherichia coli*,[5] paramecium,[6] phycomyces,[7] the rotifer (C. Levinthal, oral communication), the nematode (S. Brenner, oral communication), and the mouse.[8,9]

The fruit fly, *Drosophila*, represents a compromise. Its mass is roughly a geometric mean between *E coli* and man. *Escherichia coli* could be regarded as akin to a single neuron, since it does exhibit behavioral reactions, while man has about 10^{12}; *Drosophila*, with its 10^5, is again halfway between logarithmically speaking. The number of genes is around 10^3 for *E coli*, 10^5 for *Drosophila*, and 10^7 for man. Similarly, the generation time for *Drosophila* is about 1,000-fold longer than for *E coli* and about one thousandth of the generation time for man. Because of its short generation time and small size, plus the fact that it can be raised on simple laboratory food, *Drosophila* was chosen by the school of genetics that flourished half a century ago. The lessons learned from this model organism about the linkage of genes into linear arrays on the chromosomes, the production of mutations by x-rays and chemicals, recombination of genes by crossing over, sex determination by X and Y chromosomes, and the role of genes in development carry over almost directly to human genetics, although there are, of course, variations in detail.

While the fly's nervous system differs vastly from ours, it does work via neurons, synapses, and transmitter molecules, and its development is dictated by genes. A fly has highly developed senses of sight, hearing, taste, smell, gravity, and time. While it does not do everything that man does, it can do a few things that we cannot, such as fly or stand on the ceiling. One must not underestimate the little creature. Perhaps you have seen the remarkable film, "Hellstrom's Chronicle," of which the theme was that the insects were here well before man's arrival and already have seen the dinosaurs come and go. It should be recalled that the fly is not

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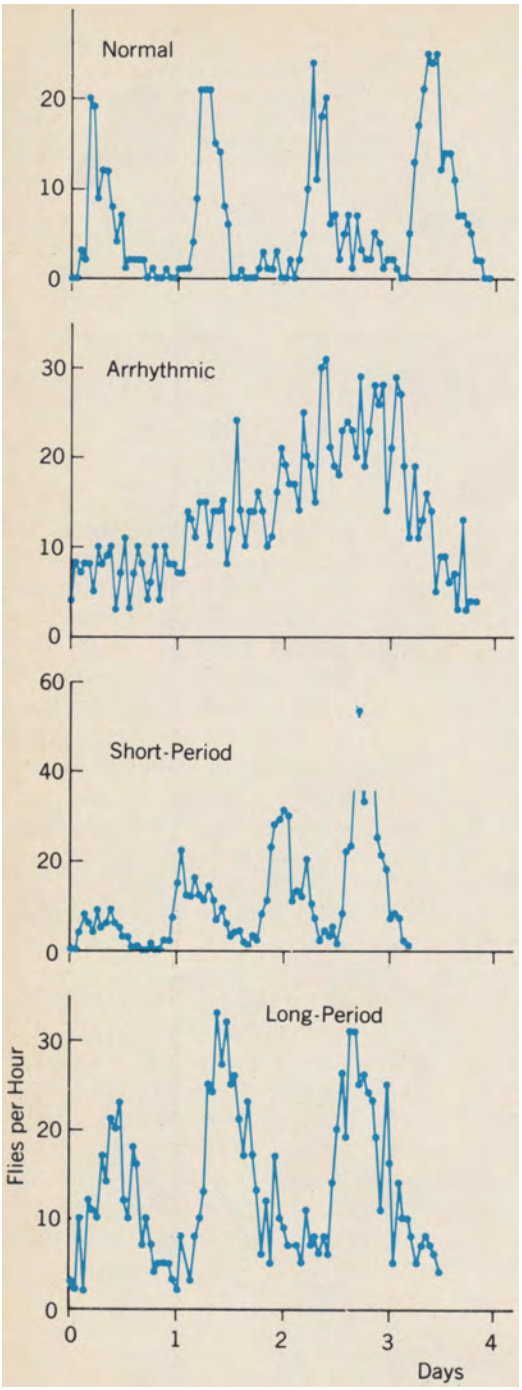


Fig 1.—Rhythm of eclosion of adult flies from population of pupae in constant darkness, showing curves for normal and rhythm mutant flies. (From Konopka and Benzer[15])

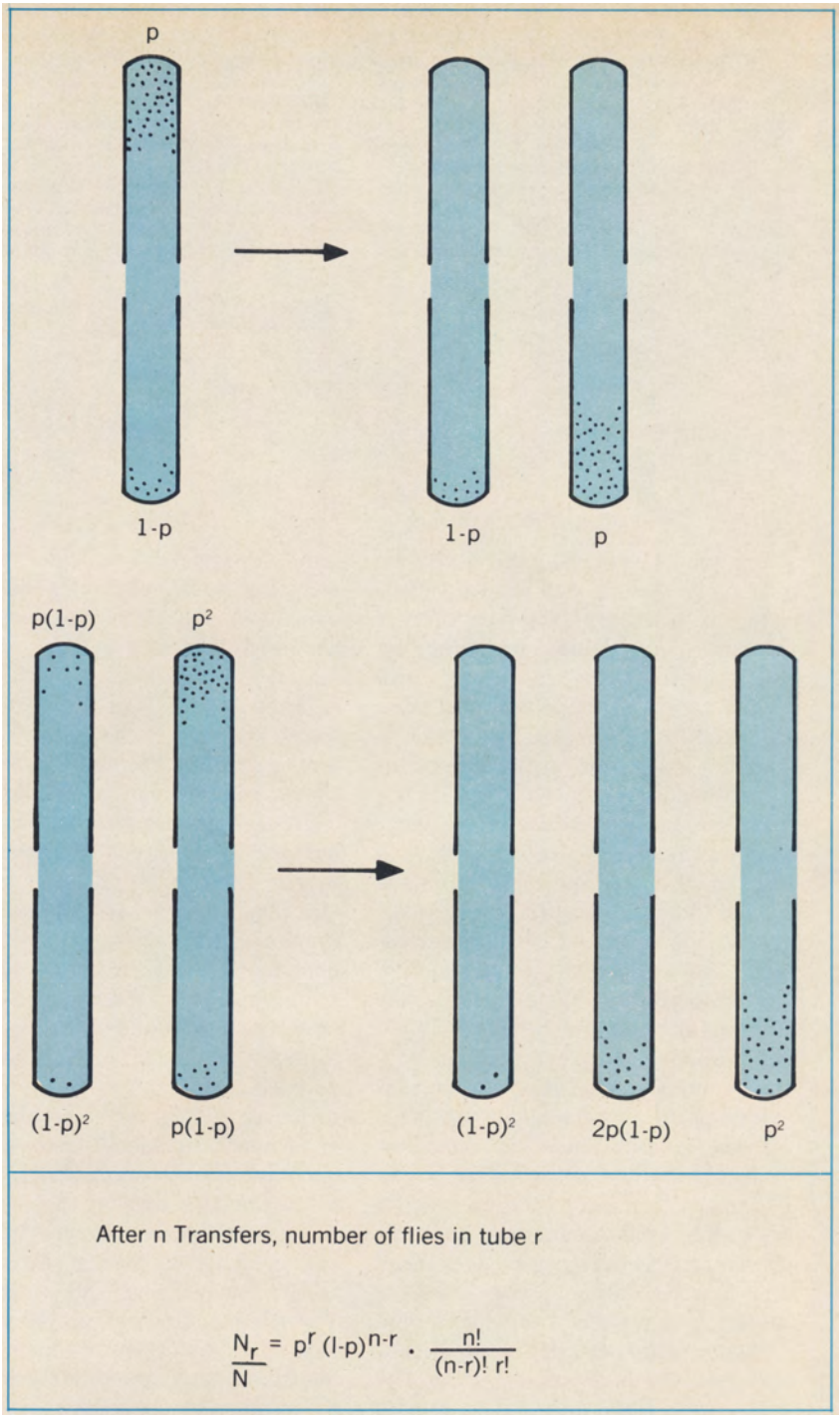


Fig 2.—Countercurrent distribution scheme.[16] Flies are started at one end of tube pair. Responders and nonresponders are separated by shifting one of tubes, then flies are returned to starting end, and new cycle is begun. Multiple transfers produce distribution according to probability of response. This method can be adapted to various stimuli.

an evolutionary antecedent of man, but is high up on the invertebrate branch of the phylogenetic tree. Some of its independently evolved behavioral patterns[10] are not unlike our own.

For example, sexual courtship in *Drosophila* begins with an encounter between individuals of opposite sex. The male, spying a female, orients toward her, faces her head from one side, and holds out and vibrates one wing, producing a species-specific song.[11] After this overture, the male usually runs to the other side and repeats the performance with the other wing, always using the wing closer to the female's head. There follows a series of steps that are only too embarrassingly anthropomorphic. In both fly and man, sexual courtship is a chain of action patterns, each dependent on the previous one for activation of the nervous system to be re-

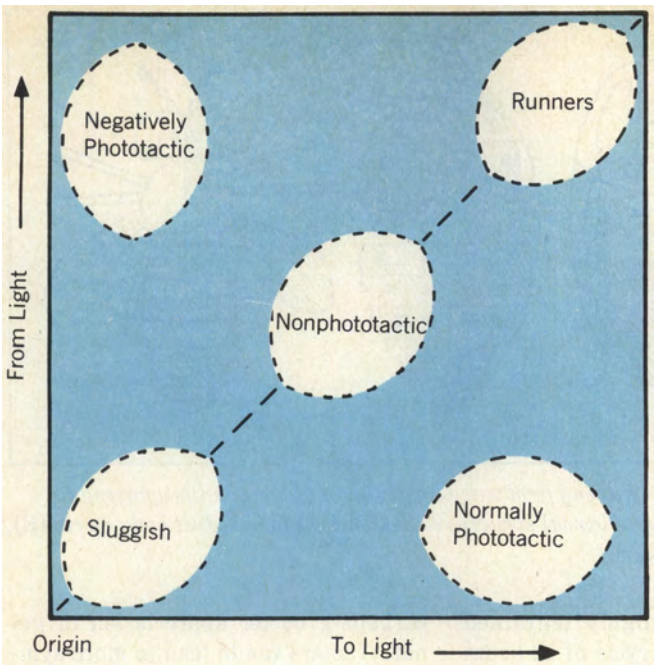
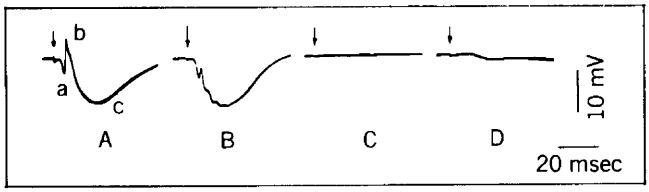


Fig 3.—Two-dimensional "chromatography" of population of flies according to phototactic behavior. Using multiple-trial countercurrent distribution, mutagenized flies are first separated according to their movement to light. Each fraction is then separated according to movement from light. Four abnormal types are obtained.

Fig 4.—Electroretinograms of normal and visually defective flies. Stimulus (arrow) *is 20μsec strobe flash. Upward direction is corneal positive. Normal fly* (A), *showing receptor potential wave* a *plus* c, *which triggers off sharp positive peak* b. *Mutant* (B) *with normal receptor potential, but defective positive peak. Mutant* (C) *lacks any receptor potential.* ERG *typical of mutant with retinal degeneration* (D).



sponsive to the next step.

The role of the genes becomes evident in fly mutants. There exist what may be called *savoir-faire* mutants, where the males are relatively unsuccessful in courtship, due to inadequate performance of one of the steps. In a mutant known as *fruity*, the males pursue each other rather than females. A pathetic case is the mutant, *stuck*, in which the male is often unable to withdraw his penis after copulation. Obviously, most of these mutants would not stand a chance in the competitive natural environment. In the laboratory, however, they can be maintained and studied. Even genes having the most drastic effects can, if recessive, be carried in heterozygotes.

The richness of the behavioral repertoire of *Drosophila* and its genetic basis is illustrated by some of the known kinds of behavioral mutants (Table). All the types listed can be produced by altering single genes. In terms of locomotor activity, some mutants are congenitally *sluggish*. Others are *hyperkinetic*,[12] actually consuming oxygen at an abnormally high rate and dying sooner than normal flies. There are mutants that do not fly, though they have perfectly well-developed wings. In a courtship situation, such a mutant male may extend and vibrate his wings in quite the normal way, yet, when dropped off the end of a rod into open space he falls like a dead weight. Some mutants are uncoordinated; they stagger over themselves and each other. Others do not climb up a vertical surface, in contrast to normal flies which show strong negative geotaxis.

Some Behavioral Mutants of *Drosophila*

Locomotor
Sluggish
Hyperkinetic
Flightless
Uncoordinated
Nonclimbing
Response to stress
Easily shocked
Shaker
Freaked-out
Paralyzed[ts]
Parched
Circadian rhythm
Arrhythmic
Short-period
Long-period
Sexual
Savoir-faire
Fruity
Stuck
Visual
Nonphototactic
Negative phototactic
Nonoptomotor
Negative optomotor
Nerve and muscle abnormality
Photoreceptor degeneration
Lamina degeneration
Wings-up
Drop-dead

Individuals that appear quite normal in ordinary circumstances may harbor hereditary idiosyncracies that show up only under stress. An interesting example is the mutant, *easily shocked*. When subjected to a mechanical jolt, the mutant displays a syndrome not unlike an epileptic seizure: The fly takes a few faltering steps, falls on its back, flails its legs and wings wildly, and coils its abdomen under. A male exudes a droplet of fluid; a female is likely to extrude an egg. The fly then goes into a coma, lasting some minutes, after which it revives and walks around as if nothing had happened. This routine can be repeated many times. The mechanism is unknown. We do know that there exist several different genes on the X chromosome alone which, if mutated, can produce this syndrome.

Some abnormalities become manifest only under anesthesia. In working with *Drosophila*, one often anesthetizes the flies with ether for examination under the microscope. While normal flies lie quietly for five or ten minutes, mutants known as *shakers*[12] vigorously vibrate all their legs. Another type is one which we call *freaked out*, because, under the influence of ether, it performs grotesque, random gyrations. It is not inconceivable that mutants such as these could shed light on the mechanism of anesthesia, and the genetic factors involved in individual idiosyncracies.

Gene changes in flies also produce marked differences in response to ex-

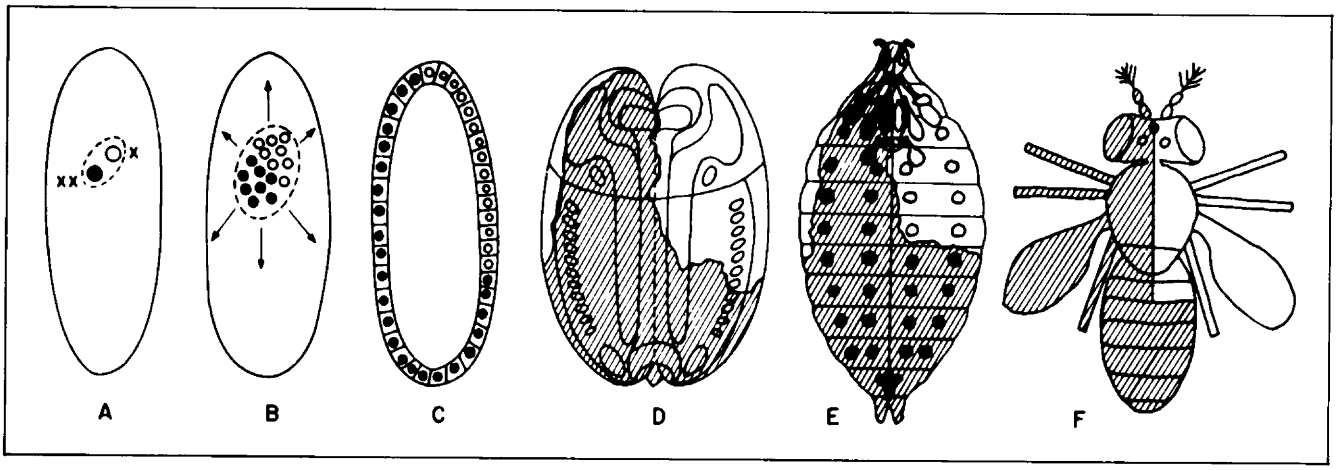


Fig 5.—Formation of mosaic fly, showing one X chromosome lost during first nuclear division (A), *nuclei migrating to surface* (B), *composite blastula* (C), *fate map of embryo* (D), *map of larval structures destined to form adult body parts* (E), *and mosaic fly after metamorphosis* (F). *(From Hotta and Benzer[19])*

tremes of temperature and humidity. A spectacular mutant is *paralyzed (temperature-sensitive),*[13] which collapses above a critical temperature, when normal flies are unaffected. When the temperature is lowered again, the mutant flies stand up and continue with business as usual. Several such mutants are now known, each with its own critical temperature. Another kind of mutant, *parched,* dies within a few minutes after being placed in a low-humidity atmosphere, whereas normal flies survive much longer. One is reminded of the sometimes remarkable variations in human preferences for atmospheric conditions. While some of those are undoubtedly due to training, it is possible that genetic components are significant in ways that are not ordinarily considered.

An important feature of behavior in a wide range of organisms is the endogenous 24-hour rhythm controlling activity, which has become personally evident to everyone in this day of jet displacement to new time zones. The fruit fly, too, shows a natural circadian (around one day) rhythm,[14] and here it is possible to clearly demonstrate the role of the genes. The name *Drosophila,* by the way, means "lover of dew." Adults normally eclose from the pupal stage around dawn, when all is moist and cool. The young fly must expand its folded wings and harden its cuticle, and it is important to time emergence carefully to minimize the risk of desiccation or easy visibility to predators until it is able to fly. The fly has, in fact, evolved a highly ingrained biological clock. In a cycle of 12 hours of light and 12 hours of darkness, adults emerge mostly during a few hours around dawn; those that miss this interval tend to wait until dawn on the following or successive days. The rhythm persists even in constant darkness (provided the pupae have previously been exposed to light); once primed, the internal clock continues to run on its natural cycle. The activity of an adult fly, once emerged, is similarly controlled by an internal clock. While the fly is maintained in constant darkness, its locomotion can be monitored by a photocell with use of infrared light which the fly cannot see. At a certain time, the fly begins to walk around for about 12 hours, then becomes very quiet, as if asleep on its feet. Next day, at the same time or within an hour or so, activity begins anew.

The genetic control of this clock is clearly shown by the fact that one can obtain mutants with abnormal rhythms,[15] or even no rhythm, as shown in Fig 1. *Arrhythmic* mutant flies eclose at arbitrary times of day. After emergence, they are typical insomniacs; when they are kept in constant darkness, their locomotor activity is spread randomly over time. A *short-period* mutant has an excellent rhythm, but runs on a natural cycle of 19 hours rather than 24. A *long-period* mutant runs on a 28-hour cycle. In a normal world, these mutants would appear always to wake up too early or too late. One need not look far to find human analogs of these types, and perhaps a better appreciation of genetic factors would lead to more sympathetic understanding of such idiosyncracies. My wife, for instance, is an early bird, while I am a night owl; we have long ago decided that there is nothing we can do about it. Each of us might, indeed, be categorized as sluggish or hyperkinetic, depending upon the time of day chosen for comparison. It is possible that genetics may be a strong component of this personality trait.

Suppose that one wishes to analyze the visual system genetically. It is possible to handle large populations of flies, treating each fly much as a molecule of behavior, and fractionate the group into normal and abnormal types. To increase the mutation rate, a mutagen such as ethyl methanesulfonate is added to sugar water and fed to male flies; this alkylating agent attacks the sperm, inducing mutations. To obtain blind mutants, for example, one can select for loss of the fly's normal response of running toward light when agitated. The progeny of mutagenized males are readily fractionated by means of a counter-current distribution technique,[16] as shown in Fig 2. This is quite analogous to partition chromatography for separating molecules between two liquid phases, except that the two phases in this case are light and darkness. The population can be "chromatographed" in two dimensions, based on multiple trials for movement toward light, then away from light. Figure 3 illustrates the various behavioral types. Normal flies

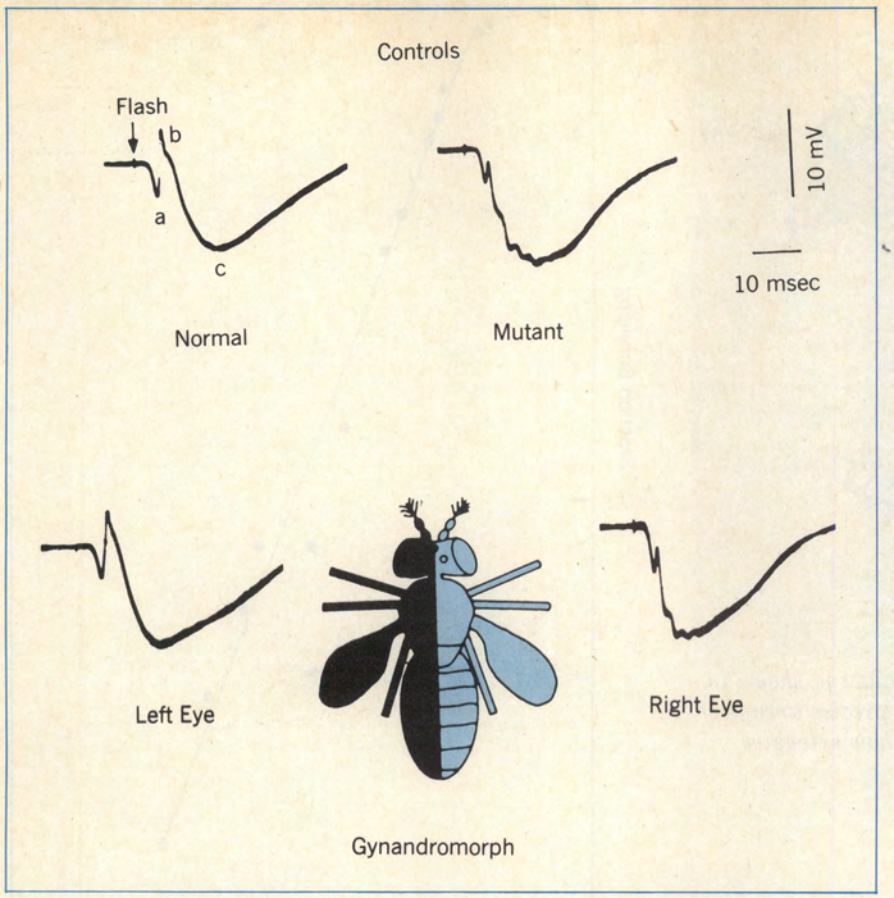


Fig 6.—Electroretinograms of mosaic fly, compared to normal and mutant controls. Black body parts have normal genotype, colored parts are mutant. Mutant eye produces fully defective ERG, in spite of presence of normal tissue elsewhere. (From Hotta and Benzer[19])

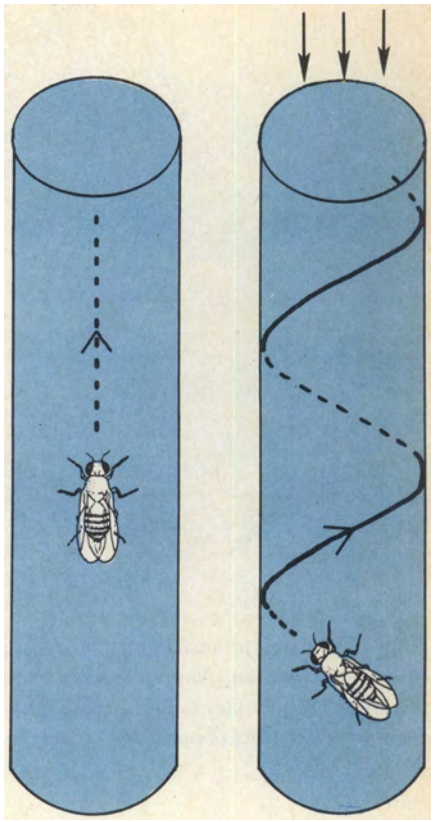


Fig 7.—Climbing path of mosaic fly with one blind eye in darkness (at left) *and with light shining from above* (at right). *(From Hotta and Benzer[19])*

consistently move toward light but not away from it, and the bulk of the progeny of mutagenized parents do just that. However, one also obtains mutants that respond differently. In fact, all of the four idiosyncratic types that could be expected from this fractionation procedure have been found. Thus, certain mutants run neither toward light nor from it. These sluggish types in some cases show cases show obvious anatomical defects, but in others they appear outwardly normal. Some mutants are *runners,* and move very vigorously whether to or from light (or even in the dark). One also obtains the reverse of normal, ie, negatively phototactic. Finally, there is the kind that acts simply *nonphototactic,* showing normal tendency to walk, but irrespective of whether it is to or from light. These flies behave in light just as do normal flies in the dark, suggesting that they are blind.

In ophthalmological clinics, the electroretinogram (ERG) is a diagnostic tool for analyzing visual defects. This procedure is easily performed on the fly's eye which, incidentally, gives signals much larger than does the human eye. Figure 4 shows the normal ERG and those of some nonphototactic mutants, measured by my colleague, Y. Hotta. In some cases, the photoreceptor cell responds, but fails to trigger off excitation of the next step in the visual pathway.[17,18] In others, the genetic lesion affects the response of the primary photoreceptor cells so that no signal at all is observed. In another type, the signal is small and greatly delayed. Histological examination of the latter reveals that the photoreceptor elements present in the young adult degenerate with age, not unlike genetic conditions known in man. Thus, the fly's eye may provide a model system for various kinds of blindness. Although many different mechanisms could result in such disorders, mutant material provides perturbations which can be used to analyze normal function.

A basic difficulty in pathology, whether in fly or man, is to identify the primary defective focus that causes an observed condition. This focus may lie in an altogether different region of the body from the affected organ. Certain cases of retinal degeneration in man, for instance, are due not at all to a defect in the eye, but are caused by insufficient absorption of dietary vitamin A by the gut. This question recalls the familiar conflict in medical history between humoralism and solidism. A neat way to make the test would be to excise the defective organ and transplant it in place of the corresponding one in a normal individual. If it is a matter of a circulating humor, the transplanted organ should function normally. If the solid organ is at fault, it should still be defective in a normal host.

In *Drosophila,* one can, in effect, do

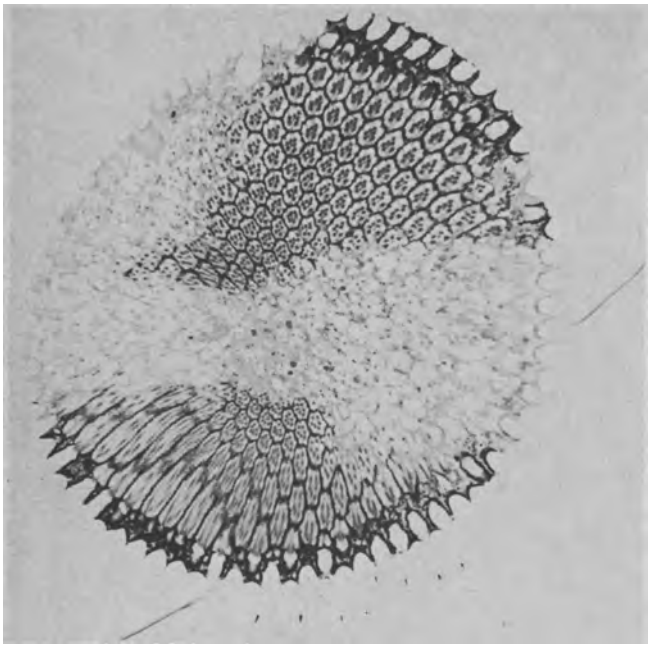


Fig 8.—Mosaicism within single Drosophila *eye, shown in tangenital section. Normal areas show precise arrays of photoreceptor elements; mutant areas show extensive degeneration (toluidine blue, ×200).*

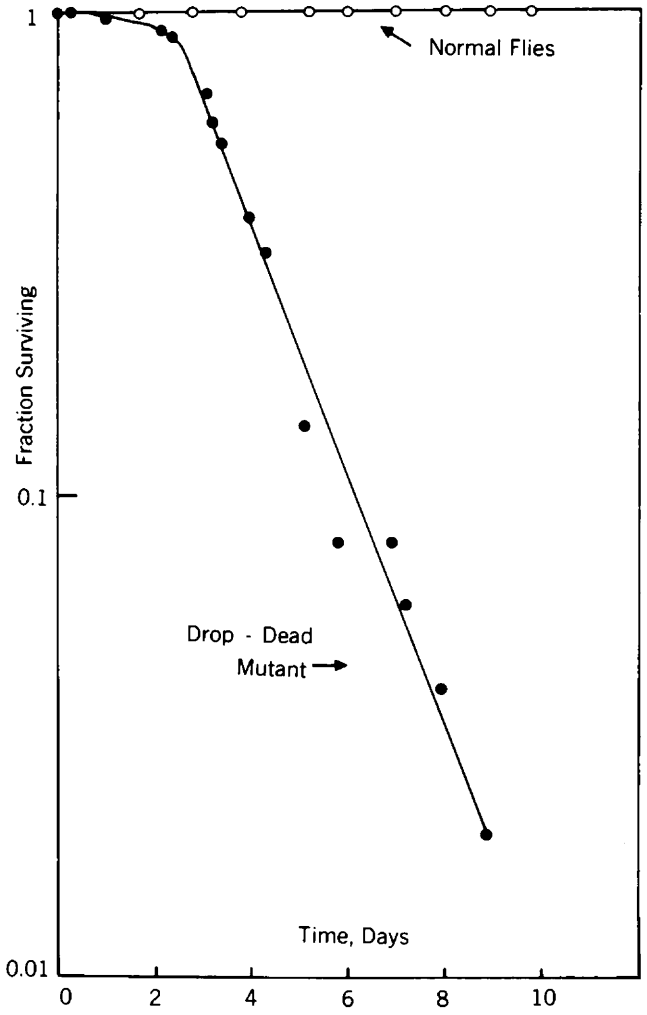


Fig 9.—Survival curve of drop-dead mutant flies, compared to normal.

precisely such experiments by using genetic techniques; mosaic individuals can be produced that are composed of parts having different genotypes. One way of doing this is to utilize a fly strain which has a special ring X chromosome that tends to get lost during the first nuclear division of the developing egg. This is illustrated in Fig 5. If the experiment starts with female eggs which have this ring for one of its two X chromosomes, in a certain fraction of the embryos the first division produces one daughter nucleus which still has both X chromosomes and another that contains only one X chromosome. In *Drosophila*, the latter (XO) type nucleus produces male tissues. The nuclei divide in a kind of syncytium and, after about a dozen divisions, migrate to the surface of the egg, forming a blastoderm. The groups of nuclei stay roughly intact, so that the XX (female) group tends to populate one area of the surface, while the XO (male) group covers the remainder. Since, in *Drosophila*, the orientation of the first nuclear division spindle is arbitrary with respect to the axes of the egg, the dividing line between XX and XO tissues can cut the embryo in any way, in some cases longitudinally down the middle, in others transversely, or at an angle. When, after larval growth and metamorphosis, the adult fly emerges, it is a gynandromorph, ie, consists of female and male parts.

To adapt this system to the problem at hand, given a recessive behavioral gene, that gene is recombined on the (nonring) X chromosome with other recessive marker genes that affect phenotypes visible in the adult, such as white eyes, yellow body color, and forked bristles. In the XX body parts, these marker genes will be dominated by the corresponding normal genes on the second X chromosome, but in the XO parts, the mutations will be expressed. Examination of the surface of the fly identifies the parts that are normal and those in which the mutant genes have been uncovered. One can then select from among the random gynandromorphs produced ones in which the dividing line falls in desired ways. Thus, individuals can be obtained which have a normal head on a mutant body, or vice versa, or even flies with one mutant eye and one normal one.

This has been done with various visually defective mutants, using the ERG to test the function of each eye. Figure 6 shows the typical results found with many ERG mutants, namely, that the ERG of the mutant eye is completely abnormal while the normal eye functions properly.[19] One can even choose gynandromorphs in which all the body of the fly is normal, except for one eye, and the mutant eye still shows a defective ERG. This immediately wipes out the humoral theory for these mutants, saving one from the futility of hunting in the cir-

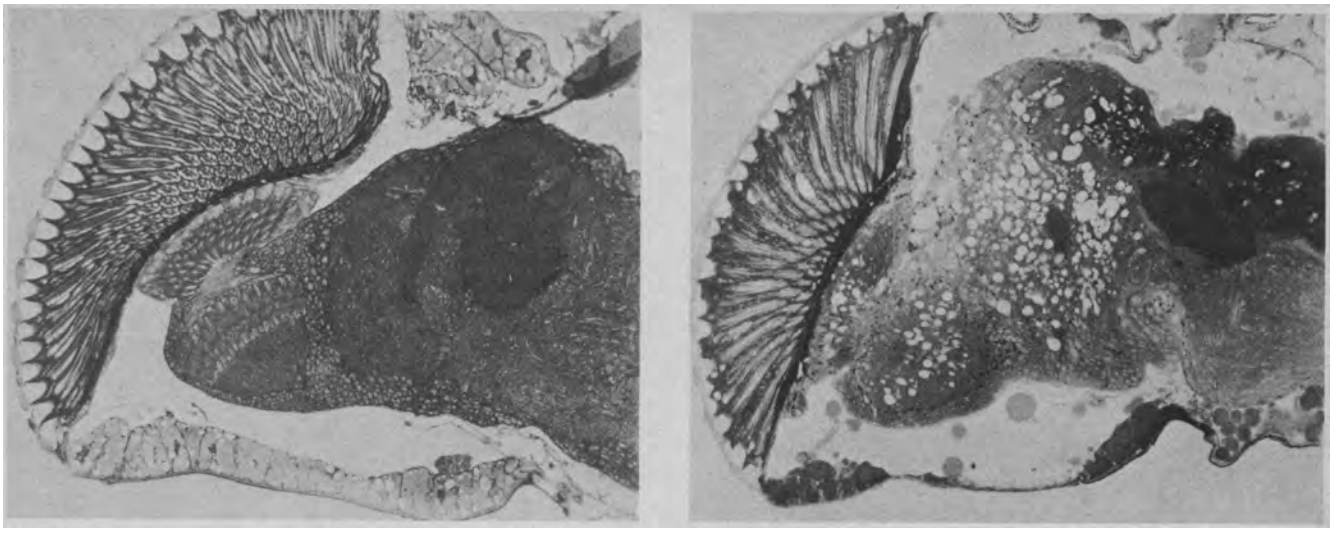


Fig 10.—Horizontal sections through head of Drosophila, *showing eye* (at extreme left), *optic ganglia* (at left of center), *and brain.* Left, *Normal fly.* Right, *Drop-dead mutant, at stage of pronounced staggering (toluidine blue, ×180).*

culation for an essential substance. The blindness may still be due to a biochemical defect, but that defect must be autonomous within the eye itself.

The behavior of flies with one good and one bad eye is amusing to observe. A normal fly, when placed in a vertical tube in the dark, climbs more-or-less straight up, utilizing gravity as a cue. If there is a light source on top, the fly still climbs straight up, since the phototactic orientation response, which a fly achieves by moving in such a direction that the light intensities on the two eyes are kept equal, indicates a direction consistent with the gravity cue. If one now puts a 50-50 gynandromorph (one eye good, the other eye bad) into the tube in the dark, it climbs straight, as a normal fly does, since its gravity sense is unimpaired. But if a light at the top is turned on, the fly now traces a helical path, always turning the defective eye toward the light in a futile attempt to balance input signals (Fig 7). Thus, if the right eye is the bad one, the fly traces a right-handed helix; if the left eye is defective, one observes a left-handed helix. Sometimes, purely for reasons of nostalgia, we put two flies in, and obtain a double helix.

A single eye can be subdivided by mosaicism, as illustrated in Fig 8. The compound eye of *Drosophila* consists of around 800 ommatidia, each of which comprises eight photoreceptor cells arranged in a precise geometrical arrangement. In the mutant used, the photoreceptor cells undergo extensive degeneration within a few days after the fly emerges. Note that degenerated and normal areas can exist contiguously in a mosaic eye. This demonstrates a high degree of autonomy of the defect. Thus, degeneration can be used as a cell marker to trace lineage of the photoreceptor cells in the development of the eye.

The gynandromorph technique also can be used to good effect in analyzing behavioral phenomena. For instance, where is the origin of the circadian rhythm in the fly? Some preliminary work has been done with gynandromorphs (R.J. Konopka, unpublished data) in which part of the body has one rhythm gene combination, while the rest of the body has a different one. The results indicate that the clock is closely associated with the head; a fly with a mutant head runs on a mutant rhythm, even if all the rest of the body is normal. An especially interesting case arises when half the head is normal, the other half mutant. In such "split-brain" flies, the rhythms observed in some cases seem to be neither one nor the other but more complex. Just as Roger Sperry has done for human split-brain subjects, it may prove possible to learn how the two "hemispheres" of the fly brain interact to produce normal behavior.

The pursuit of the primary focus of a behavioral phenotype may lead to unexpected results. One mutant, which we call *wings-up*, raises its wings shortly after emergence to a position perpendicular to the body axis, and keeps them permanently in that position. Is this a defect in the wing itself, its articulation, the wing-controlling muscles, or a "psychological" quirk of the nervous system? Study of mosaic flies shows that the character is more closely associated with the thorax of the fly than with the head or abdomen. However, it does not reside in the wings or, indeed, anywhere on the thorax cuticle, for in some mosaics the entire thorax surface may be normal, yet the wings are held up, and vice versa. One must bear in mind that the markers ordinarily used for identification of the parts of mosaic flies are on the outside of the fly. The genotype of the surface is not necessarily the same as the underlying tissues, which arise from different, albeit nearby regions of the embryo. Once the general region of the thorax was implicated, histological study of the mutant thorax was done, revealing that, indeed, certain thoracic muscles were defective. In the fly, the raising and lowering of the wings during normal flight occurs indirectly by alternate action of vertical and longitudinal muscles that change the shape of the thorax. In the wings-up mutant, all these indirect flight muscles are defective, while other muscles are quite normal.

Electron microscopy shows an almost complete lack of myofibrils in the affected muscles. In flies heterozygous for this gene, myofibrils are present, but in contrast to the very precise striations in normal flight muscle, the Z-bands are highly irregular, as if there were a deficit in the amount of Z-band substance produced. If this is the case, it calls to mind the syndrome in man of nemaline myopathy, in which the converse seems to apply, the genetic defect causing an excess of Z-band molecules.

Another recently discovered mutant of interest is one we call *drop-dead*. For the first day or two after emergence, the adults show normal behavior, such as walking, flying, geotaxis, phototaxis, and mating. At some unpredictable time, each individual becomes less active, begins to walk in an uncoordinated manner, falls on its back with limbs struggling, and dies. While the transition from apparently normal behavior to death occurs within only several hours, the time of onset of the syndrome is highly variable; after an initial period, the number of surviving flies drops exponentially with a half-life of about two days, as shown in Fig 9. It is as if some random event triggers off a cataclysm. The penetrance of the gene is complete; virtually all mutant individuals are dead long before any mortality occurs in normal flies. Death rate depends surprisingly little on temperature (between 18 C and 29 C) and is the same for hemizygous males and homozygous females. Heterozygous females are normal; the gene is recessive.

Mosaic analysis shows that whether a fly drops dead or not is most closely correlated with the genotype of the head, rather than the thorax or abdomen. However, there do occur occasional mosaics where the entire head surface is normal, yet the fly drops dead, and vice versa. This suggests that we should look inside the head to the brain. Histological examination of drop-dead mutant flies, fixed before staggering has set in, shows fairly normal appearance of the brain and other internal structures of the head, even for flies which survived after many of their siblings had died. However, whenever a fly that is already demonstrating staggering symptoms is examined, the brain is found to be shot full of holes (Fig 10). The holes tend to be concentrated around certain regions of the brain, but extend also into surrounding areas, including the optic ganglia. Other parts of the nervous system, such as the thoracic ganglion, appear normal.

This syndrome recalls the many kinds of hereditary brain degeneration in man. For instance, the gene for Huntington's disease leads to degeneration which appears to start in a specific brain region and is followed by more general deterioration, production of involuntary movements, incapacitation, and death. Although the gene is sooner or later expressed in all individuals carrying it, the age of onset of symptoms is highly variable. In fact, the distribution of incidence vs age for drop-dead is roughly similar to that for Huntington's disease, one day in the life of a drop-dead fly being roughly equivalent to a decade for an affected human. It has sometimes been suggested that this variability in onset of Huntington's disease may be due to the effects of other, modifier, genes, as indeed it might be. However, from the case of drop-dead mutants, it is clear that, even with constant genetic background, the effect of a single gene can become manifest at very different times in different individuals. One must not, of course, push analogies such as these too far. The gene for Huntington's disease is dominant and autosomal, while drop-dead is recessive and sex-linked, and, needless to say, a fly is not a man.

In summary, gene changes can alter behavior in many different ways, and by very diverse mechanisms, by affecting the development and function of sense organs, the central nervous system, or motor output. Mutations provide an incisive tool for producing perturbations by which the normal system may be dissected and analyzed. Genetic tricks such as production of mosaic individuals are powerful in pinpointing the relevant components. Experience thus far with the fly as a model system for unraveling the path from the gene to behavior is encouraging. In any case, it is fun.

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