the first two experiments found no changes in nociceptive responding 24 hours after inescapable shock exposure in the absence of reexposure. We thus examined the effects of inescapable shock under those conditions in which long-term analgesia can be observed.

As in experiments 1 and 2, we found no differences in the single-crossing shuttle-box trials (Table 2). The effect of shock on tail-flick latency does depend upon whether the subject can control shock. The group that could originally escape shock did not differ from the unshocked controls, whereas the yoked group exhibited analgesia. Analysis of variance revealed a reliable effect of preliminary treatment [$F(2,18) = 12.97$, $P < .001$]. Newman-Keuls tests ($P = .05$) showed that the escape and no-shock groups did not differ, and both responded more rapidly than the yoked group.

These results have implications for the mechanisms that produce the effects of learned helplessness and stress analgesia. With regard to learned helplessness experiments, our results potentially explain why inescapably shocked subjects are less active in the presence of shock: Shock may simply be less painful. Antinociceptive processes will not explain all of the effects of uncontrollable shock, however. In particular, they cannot explain why an associative deficit of the sort predicted by the learned helplessness hypothesis occurs (*3*, *4*).

The implications of our results for the mechanism or mechanisms producing analgesia are also important. The results of the final experiment indicate that long-term analgesic effects may not be a simple consequence of exposure to an aversive stimulus. Only inescapable shock produced a nociceptive change 24 hours later. Thus the psychological dimension of uncontrollability may determine stress-induced analgesic reactions. The same need not be true of the short-term stress-induced analgesias, however, which do not require reexposure to the stressor for their occurrence. There may be two or more different analgesic effects produced by different mechanisms.

It might appear that there are poor grounds for arguing that the reinstatement of analgesia occurs only after inescapable shock. Only experiment 3 varied control over shock, and reexposure groups were not compared with no-reexposure groups. But in the first two experiments we found no long-term analgesic reactions after inescapable shock unless brief reexposure to shock was given. Moreover, groups exposed to inescapable shock of fixed duration and yoked controls exposed to inescapable shock have not been found to differ on any measure (*1*). Thus, it is likely that, had we used no reexposure groups in experiment 3, there would have been no analgesic reaction in yoked subjects.

The nature of the mechanisms whereby uncontrollable shock produces changes in nociception remains open. A number of investigators (*5*, *6*) have suggested that the short-term stress-induced analgesia is mediated by the release of endorphins. Our longer-term effects may be produced because exposure to uncontrollable events sensitizes the system or systems responsible for controlling endorphins. Thus reexposure to shock might lead to the release of these analgesia-producing substances. It should be emphasized that our data indicate that if the opiate peptides are involved, the systems controlling the opiate peptides are regulated by the controllability of the stressor. This possibility suggests a potentially important psychological role for the endorphins. When an organism encounters aversive stimuli, pain motivates coping behaviors. If the aversive stimulus is uncontrollable, the continuation of active coping attempts may not be beneficial, since it would deplete bodily energy resources. If escape is not possible, it would be more adaptive to conserve these resources until active coping might be successful (*7*). Endogenous pain regulatory systems could facilitate conservation by reducing coping attempts directly by reducing the motivation to engage in these behaviors.

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Learning in Normal and Mutant *Drosophila* Larvae

Abstract. *Adult* Drosophila melanogaster *have previously been conditioned with shock to avoid various odors. In these experiments, larvae also sensed airborne odorants, responded to electric shock, and learned. Larval behavior paralleled adult behavior for (i) a mutant, smellblind, which failed to respond to odorants; (ii) three mutants, dunce, turnip, and cabbage, which were deficient in olfactory learning ability; and (iii) a mutant heterozygote, turnip/+, which learned but also forgot rapidly.*

Populations of fruit flies can be trained to avoid an odor by being shocked in its presence (*1*, *2*). We wondered whether the larva, with its simpler brain, could also learn. An earlier report of *Drosophila* larval conditioning retained through metamorphosis (*3*) was shown to be attributable to simple habituation (*4*). Nevertheless, larvae of another insect, *Tenebrio molitor*, have been successfully trained to several tasks (*5*, *6*). The experiments reported here indicate that *Drosophila* larvae sense and discriminate odorants, respond to electric shock reinforcement, and learn approximately as well as adult flies. Furthermore, several mutations that block learning or memory in adults cause comparable deficiencies in larvae.

Genetic stocks used were the Canton-Special (C-S) wild-type strain and four mutants derived from it. The mutant smellblind (smb^{PS542}) (*7*) and the learning-deficient mutants dunce (*8*), turnip (tur^{PS274}) (*7*, *9*), and cabbage (cab^{PS264}) (*7*) were isolated according to the mutagenesis and screening procedure of Dudai *et al.* (*8*). All flies and larvae were raised in half-pint milk bottles at 25°C on standard cornmeal medium (*10*).

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About 60 minutes before a chemotaxis or learning experiment, third-instar larvae were isolated from the medium and cleaned. Approximately 150 ml of 25 percent sucrose solution was poured into a culture bottle with growing larvae; the larvae, unable to respire, left the medium and floated to the surface of the solution. They were decanted onto nylon bolting cloth (pore size, 100 μm) (*11*), and washed with distilled water. Third-instar larvae [identified by size and the presence of protruded anterior spiracles (*12*)] were transferred with a No. 1 camel's-hair brush to a petri dish containing 1.4 percent agarose, where they crawled around the surface. A small (~1 cm^3) piece of standard cornmeal medium was placed on the dish with the larvae to prevent them from starving before the experiment. Third-instar larvae were used unless otherwise specified. When first-instar larvae were to be trained, synchronous cultures were set up, and larvae were harvested from the surface of the medium 24 to 36 hours after the eggs were laid. First-instar larvae, identified by size and absence of everted anterior spiracles, were cleaned and treated as above.

Table 1. Performance of normal C-S and dunce larvae. For the normal larvae, data are pooled from 20 experiments, and for the dunce larvae, from 10 experiments.

Odor paired with shock during training	Total larvae	Number avoiding		Fraction avoiding	
		Octanol	Amyl acetate	Octanol	Amyl acetate
		Normal larvae			
Octanol	781	513	268	0.66	0.34
Amyl acetate	794	321	473	0.40	0.60
		Dunce larvae			
Octanol	602	301	301	0.50	0.50
Amyl acetate	595	307	288	0.52	0.48

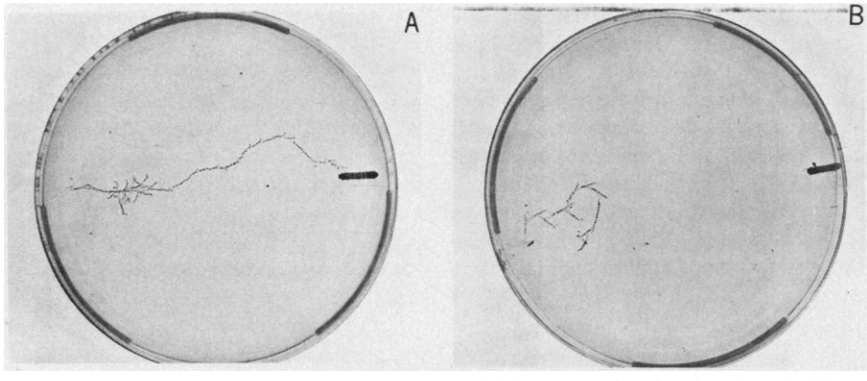

Fig. 1. Larval chemotaxis. (A) A single third-instar C-S larva was placed at the edge of a 90-mm petri plate containing 1.4 percent agarose gel opposite a capillary tube (inside diameter, 1 mm) approximately 7 mm long, sealed at one end and filled with 5 μl of the odorant 3-octanol. The larva migrated up the diffusion gradient, usually reaching the odor source within 3 minutes. The photograph was taken by inverting the plate in a photographic enlarger beam (*18*). The capillary odor source was labeled, the banded larval track in the agar can be seen, and the larva (killed with chloroform) appears as a dark spot near the mount of the odor source. (B) As in (A) after 3 minutes, but with a smellblind mutant larva.

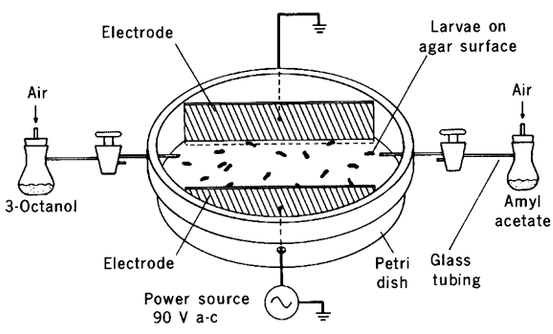

Fig. 2. Apparatus for training larvae. The gel in the plate, 1.4 percent agarose with 0.15*M* $LiCl_2$, was electrically conductive and apparently tasteless to the larvae (*19*). Pulses of electric shock were administered to the larvae by passing current between two flat brass electrodes (15 cm long, 1.5 cm high, 0.1 mm thick) stuck in opposite edges of the gel. The voltage was 90 V, 60 Hz; the electric field, ~10 V/cm, was nearly uniform in the gel between the electrodes. Pulses of 3-octanol or amyl acetate could be introduced to the dish in currents of filtered and humidified air (300 ml/min) that had passed over 10 ml of the pure odorant in a 25-ml flask.

Larvae can sense airborne odorants and are attracted to the source. This chemotactic ability can be demonstrated by placing a larva in a 90-mm petri dish containing a glass capillary tube sealed at one end and filled with a chemical odorant. When the lid is placed on the dish, a diffusion gradient of the odorant forms, and the larva migrates up the concentration gradient to the odor source (Fig. 1). Larvae also respond to electric shock. If electric current is passed through an agarose gel on which they are crawling, they twitch, writhe, and eventually migrate to regions of lower field strength. Thus *Drosophila* larvae can sense cues and reinforcement similar to those previously used to train adult flies; the larval learning paradigm was similar to the adult procedure.

For training, 80 to 100 larvae, isolated and cleaned, were transferred to a 150-mm petri dish containing electrically conductive agarose gel (Fig. 2). The lid was placed on the dish and the larvae were given a 30-second pulse of amyl acetate, administered in a current of air, and simultaneously shocked by applying a voltage across the electrodes. The lid of the dish was removed, and the larvae were rested for 90 seconds in fresh air. They then received a 30-second pulse of another odorant, 3-octanol, this time without shock, followed by 90 seconds of rest. The larvae experienced each odor three times, with shock always coupled to amyl acetate.

After training, the larvae were rested for 150 seconds in fresh air. For testing, 30 to 40 larvae from the center of the training plate were transferred with a No. 000 camel's-hair brush to the center of a 90-mm petri dish with agarose. At opposite edges of the dish were two capillary tubes, one containing amyl acetate, the other octanol. The lid was placed on the dish, and odorant concentration gradients were allowed to form; learning was indicated by the migration of a majority of the larvae toward the source of octanol, the odor not associated with shock during training.

A new group of larvae were trained as above, except that electric shock was paired with octanol. In both cases normal C-S larvae avoided the odor paired with shock during their training (Fig. 3;

Table 1). As with adult flies, the index of learning Λ was defined as the fraction of the population avoiding the shock-associated odor minus the fraction avoiding the control odor, averaged for the two halves of an experiment. For the 20 experiments in Table 1, the mean Λ was .26 ± .02, which is comparable to scores of C-S adults [.34 ± .03 (*1*)]. First-instar C-S larvae can also learn: Λ = .20 ± .02.

The selective avoidance behavior appears to be genuine learning. The two-part experimental design in which larvae are trained to opposite odors eliminates odor bias and sensitization as explanations for the results. Other possible artifacts were excluded by separate controls. If larvae were exposed to three 30-second pulses of either octanol or amyl acetate (Fig. 2), they showed normal chemotactic ability when tested immediately afterward. Therefore, habituation or sensory adaptation are negligible and cannot explain the selective odor avoidance. Other experiments, in which larvae were tested immediately after electric shock, showed that their locomotor and chemotactic abilities were unaffected by the shock of reinforcement.

Genetic alterations can disrupt learning ability in both larvae and adults. Three different (complementing) X-linked mutations—dunce, turnip, and cabbage—block learning by adult flies in the basic olfactory paradigm of Quinn *et al.* (*1*); adult Λ scores are, respectively, .04 ± .02 (*8*), .06 ± .03 (*7*) and .02 ± .01 (*7*). Third-instar larvae of the mutants also failed to learn (Table 2). The mutations do not act simply by blocking larval sensory or motor capabilities. Mutant larvae all responded normally to shock reinforcement; they twitched when current was passed through their medium, and they migrated to regions of low field strength. Their ability to sense the odor cues (Fig. 2) was also normal. Thus, in the mutants tested so far, larval sensory and learning behavior parallels that of adult flies.

Larvae of a fourth mutant, smellblind, showed practically no chemotactic ability. Adult flies of this strain were also deficient in olfactory ability (*13*) as measured in a T maze [figure 3 in (*8*)]. This parallel deficiency at different stages was not expected, because in dipterans the olfactory end organs in the larval cuticle are apparently sloughed off during metamorphosis and replaced with receptors of a different morphological type (*14, 15*). The result with the mutant indicates that either larval and adult receptors both require the normal smb^+ gene product, or the smellblind mutation disrupts processing of olfactory information in central neural structures conserved through pupation. Other mutants with olfactory deficiencies as adults have previously been isolated and characterized (*16*); their larvae have not yet been tested.

Table 2. Learning and memory Λ scores of normal and mutant larvae. Third-instar larvae, mixed males and females, were used unless otherwise specified. Values are means ± standard errors for ten experiments. Learning was tested 2.5 minutes after training. In memory experiments, the larvae were left for 15 minutes in clean air on the training plate before being tested.

Larval genotype	Learning	Memory
C-S	.26 ± .02*	.11 ± .01
C-S†	.21 ± .02	.14 ± .02
C-S‡	.20 ± .02	
dunce	−.02 ± .02	
dunce‡	.02 ± .02	
cabbage	−.02 ± .02	
turnip	−.06 ± .03	
turnip/+†	.24 ± .01	−.02 ± .02
amnesiac		.09 ± .01

*Twenty experiments. †Females. ‡First instar.

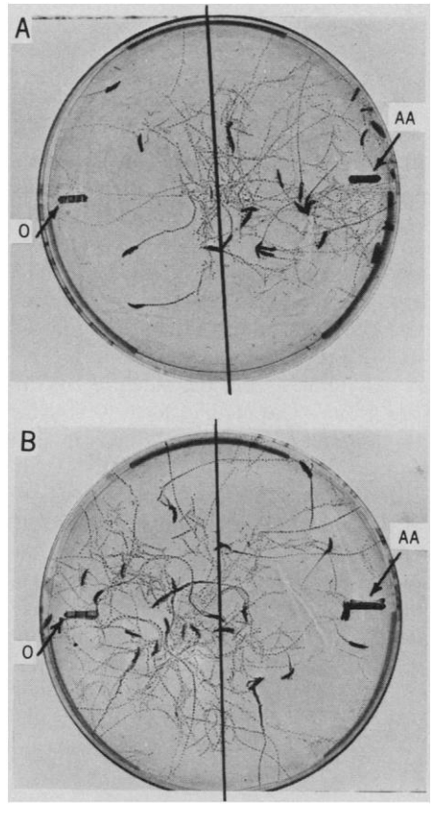

Fig. 3. Testing for learning. Capillary sources of odors 3-octanol (*O*) and amyl acetate (*AA*) were at opposite edges of the plate. After 1 minute the larvae were killed with chloroform; a diameter line was drawn on the lid between the two odor sources; and larvae on each half of the plate were counted. Photographs were made as with Fig. 1. (A) Larvae trained to avoid octanol. (B) Larvae trained to avoid amyl acetate.

Larvae apparently forget more quickly than adult flies. Expression of learned behavior decays to half its initial value after 15 minutes (Λ = .11 ± .01) and is undetectable at 30 minutes. In contrast, adults express most of their original learned behavior an hour after training, and some memory persists as long as 6 hours (*1, 2*). This disparity in retention spans could conceivably be due to differences between larval and adult learning paradigms, which are similar but not identical. Nevertheless, the rapid memory decay in larvae is striking. We believe that the difference between larval and adult retention spans is probably intrinsic and that the lengthened adult span results from anatomical or metabolic changes in *Drosophila*'s nervous system during metamorphosis.

We wanted to find out whether mutations would have corresponding effects on larval and adult memory. The most carefully characterized memory mutant amnesiac (*9*), gives an uninformative answer; amnesiac larvae remember as well as normal larvae, but both forget as fast as amensiac adults, making it difficult to say whether the mutation affects larval brains (Table 2). Adult flies heterozygous for the turnip mutation forget more rapidly still; memory is undetectable 15 minutes after training (*9*). Larval turnip/+ heterozygotes show correspondingly rapid memory decay; 15 minutes after training, Λ was −.02 ± .02.

Our results show that learning and brief memory retention are mediated by neural structures already present in first-instar larvae, which may be preserved through metamorphosis (*17*). The products of the dunce, turnip, and cabbage genes function by the third instar (by the first instar in the case of dunce). These findings may have practical value since the search for biochemical or anatomical abnormalities caused by the mutations should be easier with larvae than with adults. Larval brains are simpler, more compact, and easier to isolate from other tissues.

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17. Apparently most of the larval brain is conserved through pupation. The protocerebrum and deutocerebrum (antennal lobes) and the subesophageal and thoracic ganglia retain their general morphology and most of their larval neurons. New neurons are added in all structures, however, and the entire optic ganglion complex is generated de novo during metamorphosis [(*12*, → K. P. White and D. R. Kankel, *Dev. Biol.* **65**, 296 (1978)]. Axonal and dendritic branching patterns of cells may also change during metamorphosis [J. W. Truman and S. E. Reiss, *Science* **192**, 477 (19 → G. B. Casaday and J. M. Camhi, *J. Comp. Physiol.* **112**, 143 (1976)]. Larvae of *Tenebrio molitor* can be trained, and the memory is preserved through metamorphosis to be expressed in the adults (*5*).
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19. Chemoreceptors in adult *Calliphora* and *Drosophila* are insensitive to 0.5*M* L → [C. J. den Otter, *J. Insect Physiol.* **18**, 109 (1972); G. Pollack, E. O. Aceves-Piña, W. G. Quinn, unpublished data]. Larvae are also behaviorally insensitive to this salt in chemotaxis tests. Third-instar larvae, placed on a petri dish (Falcon 1003) containing equal semicircular sectors of agarose and agarose + 0.5*M* LiCl, distributed themselves randomly; .52 ± .02 of the larvae were on the LiCl sector after 15 minutes (ten experiments).
20. We thank S. Ward for helpful discussion and S. Benzer for his observation that larvae respond to shock. We are grateful to friends in the Benzer laboratory and to M. Ginder and J. Hall for comments on the manuscript. Preliminary experiments suggesting that larvae could learn were conducted by J. P. Corsones. We used equipment made available by the Whitehall Foundation. E.O.A.-P. was a fellow of CONACYT of Mexico. Supported by NSF grant BNS 75-00474 and NIH grant GM 25578.

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Prednisone Therapy and Birth Weight

Reinisch *et al.* (*1*) reported a retardation of intrauterine fetal growth in infertile women treated with 10 mg of prednisone daily prior to conception and throughout pregnancy. These data were widely quoted in the news media and interpreted as evidence of potential danger to the offspring. Others have reported on the use of prednisone for induction of ovulation and alleviation of female infertility, but continuation of therapy during gestation was not advocated (*2*). We examined the question whether administration of prednisone to infertile women, when discontinued after confirmation of conception, will also result in a reduction of birth weight.

Birth weight and duration of pregnancy were available for 251 births (Table 1) from women evaluated for infertility in our clinic. The data permitted a comparison of offspring of mothers receiving prednisone, prednisone and clomiphene citrate, clomiphene citrate, other therapeutic modalities (for example, low-dose estrogen, human menopausal gonadotropin, human chorionic gonadotropin, thyroid hormone), or no treatment. Mean birth weights and duration of pregnancy were comparable in all groups. One-way analysis of variance and Duncan's multiple range test showed no statistical differences among means, or differences from the mean of the entire group. The median birth weight for term infants in the United States in 1975 was reported to be 7.31 pounds (*3*). In 1978, the mean weight of all infants born at Hermann Hospital, Houston, was 7.10 pounds (*4*), remarkably close to the mean birth weights in Table 1 and to those reported as controls by Reinisch *et al.* (*1*). Unfortunately, since Reinisch *et al.* failed to provide standard errors for their data, statistical comparisons could not be made.

These observations suggest that administration of low-dose prednisone (5 to 10 mg daily) for therapy of infertility, if discontinued after documentation of pregnancy, does not result in a decrease in birth weight of infants.

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Table 1. Mean (± standard error) duration of pregnancy and infant birth weight in relation to therapeutic management of infertile women.

Therapy	Number of pregnancies	Birth weight (pounds)	Duration of pregnancy (days)
Prednisone	103	7.22 ± 0.12	281.2 ± 1.5
Prednisone and clomiphene citrate	49	7.00 ± 0.18	280.6 ± 2.3
Clomiphene citrate	28	7.06 ± 0.20	280.2 ± 2.6
Other	12	6.72 ± 0.51	284.4 ± 3.7
No treatment	59	7.12 ± 0.13	275.6 ± 1.8
Total	251	7.11 ± 0.08	279.7 ± 1.0

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26 June 1979

The report by Reinisch *et al.* (*1*) presents the potential harm of the administration of prednisone in a dosage of 10 mg daily to pregnant women. The implication that any dosage of any corticosteroid would have comparable harmful potential is, however, unfortunate. The authors quote in their introduction two of our reports of the beneficial effects of dosages of cortisone acetate or hydrocortisone between 2.5 mg every 8 hours and 5 mg four times daily in women with ovarian dysfunction and infertility (*2*), implying that such treatment would also be potentially harmful and that it "resulted in the exposure of large numbers of fetuses to augmented adrenal hormone levels."

Cortisone and hydrocortisone are normal adrenal hormones; prednisone is not. Doses of 5 mg of cortisone acetate or hydrocortisone four times daily, before meals and at bedtime, do not raise the plasma cortisol levels above normal at any time (*3*) and hence have none of the harmful potential that is so well known for hypercortisonism. A 10-mg dose of prednisone is equivalent to 50 mg of cortisone acetate, ten times the potency of an individual dose and over twice the potency of the total daily dosage we use.

After more than 20 years of experience with administering to women dosages of cortisone acetate or hydrocortisone of 5 mg four times daily or less, we have found absolutely no evidence of hypercortisonism with any of its harmful po-

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