can be injected with large amounts of epinephrine and norepinephrine. Cortisone, which antagonizes some effects of histamine, is reported to protect adrenalectomized rats from traumatic shock (*8*). In many cases of shock, adrenergic stimulation is probably extremely strong in the early stages before histidine decarboxylase has reached full activity; yet often the death of the animal is delayed. During long-continued infusions of epinephrine in man and some other species a strong drop in blood pressure occurs; if the infusion is abruptly terminated, shock may ensue (*9*). Finally, bacterial endotoxins produce shock closely resembling stress shock (*10*); *Escherichia coli* endoxin is an extremely strong inducer of histidine decarboxylase activity in many tissues (*3*).

Other possibilities relating the histamine-catechol amine balance to shock are that different tissues of the same animal may be injured by different amines, or, that once a cell is injured, all the amines may be toxic to it.

In the early research on shock, numerous workers considered histamine, or histamine-like substances, as likely candidates to be shock "toxin" (*11*). It has been dropped almost entirely from consideration at the present time. Some of the reasons are the following: (i) there are differences in the characteristics of stress-induced shock and shock produced by injection of histamine; (ii) the histamine content of normal muscle is too low to cause shock when the muscle is traumatized; (iii) histamine is not consistently found in blood and lymph in increased quantities during shock; (iv) antihistamines do not protect against shock.

Recent findings suggest that histamine may be newly synthesized at an increasing rate during stress, that it may act for long periods of time, that it may be formed close to, or possibly even within the cells which it stimulates, and that it is rapidly inactivated, forming metabolites for which there are no suitable analytical procedures (*7*). If these conjectures are correct, the reasons for discounting histamine as a shock "toxin" can no longer be considered valid (*12*).

RICHARD W. SCHAYER

Merck Institute for Therapeutic Research, Rahway, New Jersey

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4. Histidine decarboxylase was assayed by incubation of tissue extracts with 10 μg of C^{14} L-histidine for 3 hours at 37°C and determining the C^{14} histamine formed by addition of carrier, isolation, conversion to dibenzenesulfonylhistamine, and counting in a liquid scintillation counter. The method has been described in detail (*1*). All values for enzyme activity were recalculated so that the average of the controls is arbitrarily 100. This permits easier comparison of results of experiments done at different times and under different conditions.
5. There are at least two distinct types of histidine decarboxylase according to function; one is in mast cells and certain other unidentified cells and produces histamine which is largely bound. The second is the inducible histidine decarboxylase; its anatomical location is not known. The histidine decarboxylase in tissues of normal animals may be largely, perhaps entirely, due to the first type; hence the increase in the inducible histidine decarboxylase activity may be much greater than indicated by the data.
6. Histamine catabolism is complex in mice (*11*) and there is no satisfactory method for measuring histidine decarboxylase activity in vivo in this species. Therefore, only in vitro studies were made. In female rats histamine catabolism is simpler, and in these animals we have previously shown that results of in vitro experiments on induced histidine decarboxylase are parallel to those obtained from experiments in living animals (*1*).
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Critical Periods for the Effects of Infantile Experience on Adult Learning

Abstract. Mice were shocked with 0.1, 0.3, or 0.5 ma of current at 2 to 3, 8 to 9, or 15 to 16 days. Handled, nonshocked and nonhandled controls were also used. In adulthood each group was split into thirds and taught an avoidance response under shock of 0.3, 0.5, or 0.7 ma. The amount of shock given during infancy and adulthood, and the age at which shock occurred, were all found to have significant effects upon learning.

Several investigators have recently studied the question of critical periods in infancy (*1*). On the behavioral level, Schaefer (*2*) has reported that rats handled during the first week of life exhibit less emotionality in adulthood than animals handled at other times. Denenberg has shown that rats handled during the first 10 days of life are better avoidance learners in adulthood than rats handled during the second 10 days or the first 20 days of life (*3*), and that mice shocked at different times during early life have differential adult conditioning scores as well as different response topologies (*4*). On the physiological level, Levine and Lewis (*5*) have determined that rats manipulated (handled) at ages 2 to 5 days and 2 to 13 days exhibit significant adrenal ascorbic-acid depletion when assayed at 14 days, but that animals handled at 6 to 9 or 10 to 13 days do not show any evidence of depletion. Denenberg and Karas (*6*) used rats and mice which were either not handled at all or were handled for the first 10, the second 10, or the first 20 days of life; the groups handled for 20 days weighed the most, but animals handled for the first 10 days lived longest under conditions of total food and water deprivation.

It has also been shown that shock administered to mice at 25 days will significantly affect 50-day conditioning scores (*7*), and that shock administered on two days between the 5th and 10th days of life will lead to more rapid extinction of a learned response (*4*). However, there has been no systematic study of the relatively long-term behavioral effects of stimulation given to restricted age groups at different critical periods in infancy. We wish to describe some of the findings of such a study (*8*).

The subjects were 290 mice (strain C57BL/10Sc). They were stimulated at one of three ages: 2 to 3 days, 8 to 9 days, or 15 to 16 days. These ages are at the mid-point of the first three critical periods specified by Williams and Scott (*9*) and specified with modifications by one of us (*4*). Stimulation consisted of removing the complete litter from the home cage, placing the pups on a grid, and subjecting them to one of three levels of constant current: 0.1, 0.3, or 0.5 ma. Ten 1-second shocks were administered, with a 45-second pause between shocks. Handled, nonshocked controls (0.0 ma) were treated in the same way as shocked mice, except for lack of current on the grid. In addition, other litters served as nonhandled, nonshocked controls. All litters were weaned at 22 days and reared thereafter in small cages with littermates of like sex. At 61 days of age the 13 groups were randomly split into thirds and received avoidance learning conditioning under shock of 0.3, 0.5, or 0.7 ma. They received six trials a day for 7 days. The conditioning consisted of the sounding of a buzzer, followed 5 seconds later by shock. If the mouse made the appropriate response prior to the onset of shock, the shock did not occur and the mouse was credited with an "avoidance response."

Figure 1 presents the mean number of avoidance responses as a function of the level of shock given during adulthood for each of the three critical periods. Separate graphs are given for each level of shock given during infancy. The curve for the nonhandled, nonshocked control groups is based on the same mice in each of the graphs. With this one exception, each point of

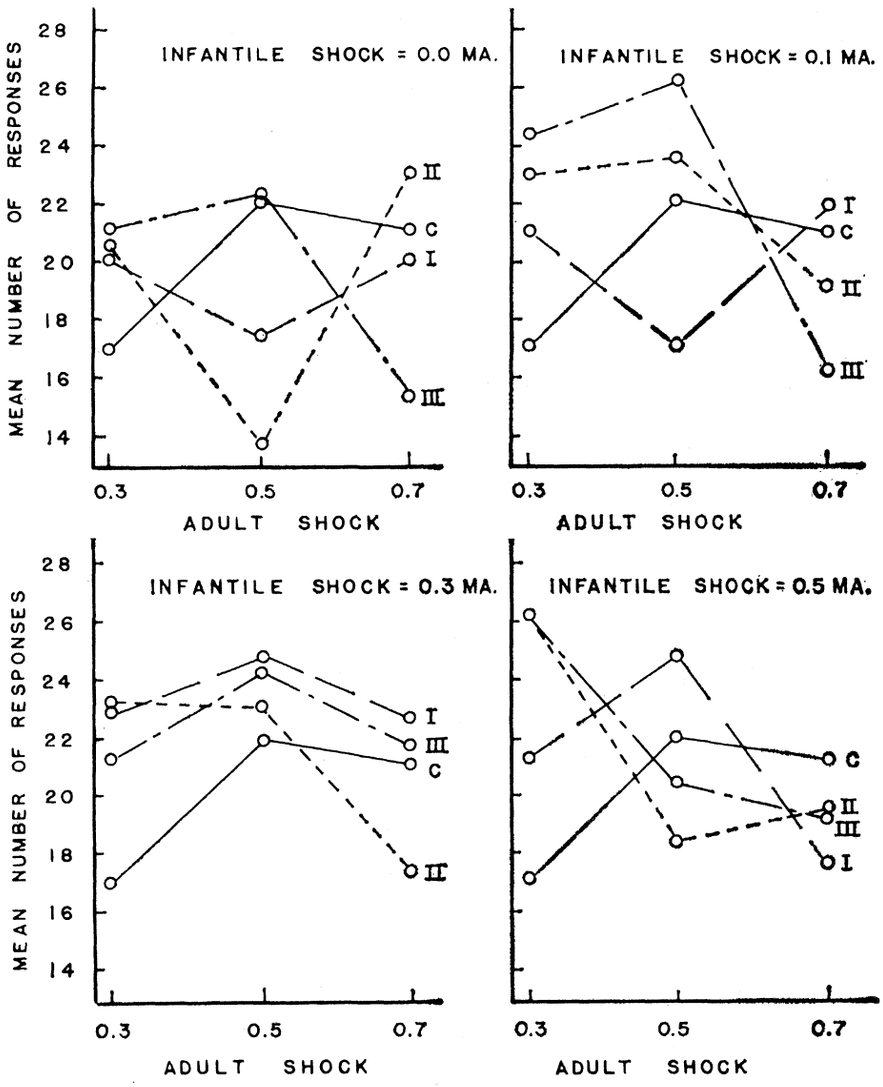

Fig. 1. Mean avoidance score as a function of intensity of shock given during adulthood for each critical period. Each level of shock given during infancy is graphed separately. (I) Critical period No. 1, 2 to 3 days; (II) critical period No. 2, 8 to 9 days; (III) critical period No. 3, 15 to 16 days; (C) nonhandled, nonshocked controls.

the curves is based upon independent groups of mice from at least two different litters, with n ranging from 7 to 11 per group. The analysis of variance of these data consisted of the main effects of critical periods (C), infantile shock (I), adult shock (A), and all interactions. The analysis showed significant differences beyond the 0.01 level for the main effects of infantile and adult shock, and for the C-A and C-I-A interactions; the I-A interaction was significant at the 0.05 level. Though C was not significant as a main effect, it was present in two of the significant interactions, and the importance of this variable was thereby established.

The above analysis did not include the three nonhandled, nonshocked control groups. Each of these control groups was compared with the 12 groups stimulated in infancy which received the same level of shock in adulthood. At 0.3 ma of shock in adulthood, all stimulated groups had significantly higher learning scores than the control group; at 0.5 ma, four of the stimulated groups scored significantly higher than the control, while four other groups scored significantly lower; at 0.7 ma, four of the stimulated groups had means which were significantly lower than that of the control group. Thus, stimulation during infancy facilitated learning at the low-adult-drive level but depressed learning at the high-drive level. This finding differs from data recently obtained with the rat, in which it was found that the effects of handling during infancy upon avoidance learning was independent of the level of shock that was employed during adulthood (*10*).

The data definitely show that the age at which stimulation occurs and the magnitude of stimulation during infancy and adulthood, singly or in combination, are major parameters which affect learning scores. Whether the stimulated mice will learn more or less rapidly than the controls is a function of particular combinations of these three variables. The data confirm the previous findings on the effects of stimulation during infancy upon learning in the mouse (*4, 7*). They are also consistent with observations of Levine and Lewis (*5*), who found that handling at ages 2 to 5 days modified the ascorbic-acid response in the rat; however, Levine and Lewis failed to find a significant effect from handling at 6 to 9 days, while we were able to obtain significant results from stimulation given at 8 to 9 days.

We should like to emphasize the extreme sensitivity of young mice to external environmental stimulation, especially at ages 2 to 3 days. It is apparent that, somehow, different levels of shock in infancy differentially affect the mouse, since the learning scores differed, even when the same level of shock was employed during adulthood. We should also like to point out that such a subtle environmental factor as transporting a mouse from its nest to the shock apparatus and back (0.0 ma) is sufficient to modify its learning scores when it is an adult. The mechanisms that bring about these behavioral changes are not known. The mouse is at markedly different stages of growth and development between 2 and 16 days of age; for example, the neuroanatomical, physiological, and perceptual motor capabilities change qualitatively during this period. Because of these major differences in maturation, it is our feeling that the same physical stimulation at these different ages has qualitatively different effects upon the developing organism.

VICTOR H. DENENBERG
ROBERT W. BELL*
Department of Psychology, Purdue University, Lafayette, Indiana

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* Present address: Department of Psychology, Allegheny College, Meadville, Pa.

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