perimental procedure of withdrawing the projected visual stimuli contingent upon sucking (SW group) failed to produce evidence for an acquired suppression of high-amplitude sucking. However, the performance of this group does provide additional control data indicating that the changes in criterion sucking in the SR group were not attributable to either generalized arousal or specific eliciting effects of visual stimulation per se. Simply presenting infants with a changing pattern of visual stimulation while they were sucking did not result in their response rates differing reliably from those of the base-line control subjects. Only those infants who were specifically reinforced with visual feedback for emitting high-amplitude sucks (SR group) showed evidence of an acquired response differentiation. The reinforcing effectiveness of the visual feedback is seen in the fact that the learned response differentiation occurred quite rapidly, and by the end of 8 minutes of reinforced training these infants showed marked proficiency in their performance with better than 0.80 of their responses meeting the conditioned response criterion.

Additional evidence for the reinforcing effects of visual feedback on sucking behavior in human infants was obtained in a subsequent experiment with 12-month infants. While the first experiment showed that visual reinforcers could be employed to modify the topography of sucking in 4-month infants, the second experiment was designed to determine whether similar reinforcement procedures could be effectively employed to reestablish sucking in infants for whom nonnutritive sucking was no longer a stable response in their behavioral repertoire. Attempts to obtain base-line reference data on nonnutritive sucking with 12-month infants indicated that better than 60 percent of the infants actively rejected the experimental nipple prior to completing a 5-minute base-line measure of sucking. The apparent aversiveness of the sucking task for these infants was reflected in the high frequency of such behaviors as "crying," "fussing," and attempts by subjects to push away the nonnutritive nipple. Thus, in the second experiment we studied the effectiveness of visual reinforcers in reestablishing sucking with 12-month infants. A second variable studied in this experiment was the effect of varying the amount of redundancy in the array of visual reinforcers on the reinforcing effectiveness of the visual feedback. Studies with infrahuman organisms have indicated that instrumental exploratory behavior increases with increasing amounts of change in the visual reinforcing event (*3*, *4*). Briefly, the second experiment compared the conditional sucking rates for two groups of ten 12-month infants who received visual reinforcers varying in the amount of redundancy. Both groups were presented with conditioning and extinction procedures similar to those employed with the SR group in the previous experiment. One group (high-redundancy group) received three replications of four chromatic stimuli as reinforcers over the two 4-minute conditioning phases (with a stimulus change each 30 seconds). The second group (low-redundancy group) was presented with a single replication of eight visual stimuli as reinforcers over these conditioning phases. The results showed that when sucking was made functional for visual feedback, both groups showed rapid acquisition of conditioned sucking during the initial 4-minute conditioning phase.

In contrast to a base-line reference group of 12-month infants, who averaged less than 15 sucks per minute over a 5-minute sucking measure, both of the experimental groups averaged better than 40 sucks per minute during the 4th minute of the initial conditioning phase. Although the two groups did not differ in their conditioned sucking rates during the initial 4-minute conditioning and 2-minute extinction phases, the effects of stimulus redundancy on the reinforcing effectiveness of the visual feedback was seen during the reconditioning and second extinction phases, with the high-redundancy group sucking at reliably higher levels than the low-redundancy group during both these phases. In contrast to the apparent satiation effects due to reinforcement which are reflected in the decreasing sucking rates for the former group during reconditioning (third and fourth replication of the set of four stimuli), infants receiving only the second replication of the set of eight stimuli during reconditioning (low-redundancy group) maintained highly stable rates of conditioned sucking. These results supported the prediction that the reinforcing effectiveness of visual feedback was reliably influenced by the amount of stimulus redundancy.

Our experiments provide support for the conclusion that effective reinforcement of motivated behavior in the young human infant is not limited to a restricted class of stimuli in his environment. In addition to nutritive reinforcers, there are other classes of stimuli, possibly in each of the sensory modalities, that are effective in strengthening instrumental behaviors in infants. Berlyne (*5*) has suggested that any stimuli that are effective in "capturing the subject's attention" can have reinforcing value in suitable circumstances. The important developmental problem is the specification of stimulus parameters which distinguish positive and negative stimuli, and distinguish reinforcing and nonreinforcing stimuli for the developing infant in each of the sensory modalities. In subsequent experiments with infants we have found that visual feedback of the type employed in these experiments was effective in supporting motivated exploratory behavior with infants as young as 3 weeks of age. Furthermore, acquisition of conditioned sucking has been demonstrated when heterogeneous auditory feedback in the form of music and human voices was employed for reinforcement.

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Tryptophan Pyrrolase Induction in Patients with Manic Depression

Mandell and Spooner (*1*) presented a graph of some biochemical data gathered from a manic-depressive patient. The authors' discussion of these data is inconsistent with the graph, and therefore is misleading. They stated that after intravenous administration of ^{14}C-tryptophan during the different clinical phases, the turnover of radioactive tryptophan to kynurenine during depression was "significantly in-

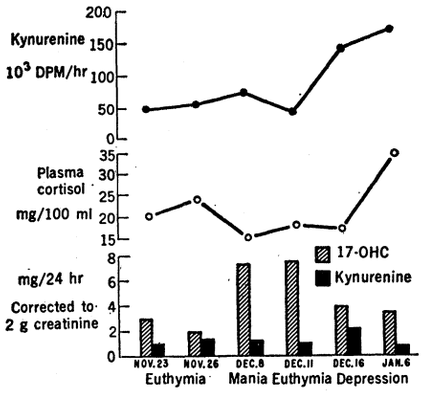

Fig. 1. Cortisol in plasma, corticoids and kynurenine in a 24-hour urine sample, and turnover of radioactive tryptophan in a patient with manic depression (adapted from *3*).

creased and associated with a rise in 17-hydroxycorticosteroids." However, the graph of urine corticoids presented shows relatively low corticoid excretion on the days of the tracer studies during depression. Mandell and Spooner could not have been referring to the mean daily corticoid excretion during depression, since for this patient it was lower than the mean excretion during mania (Table 1) (*2*).

Mandell and Spooner apparently were referring to the concentration of corticoids in the plasma rather than in the urine, a concentration which was elevated in this patient only on 6 January, the day of the second tracer study during depression (Fig. 1). This patient was one of three who were hospitalized for rapidly cycling manic depression and who were included in a large, multivariate study of manifest

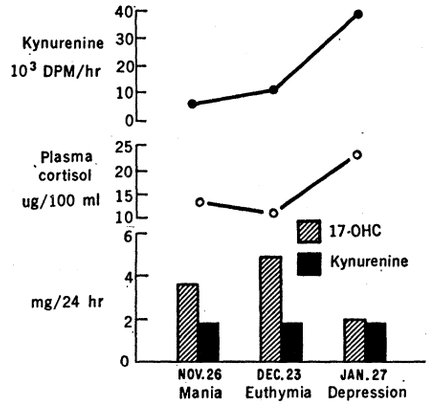

Fig. 2. Cortisol in plasma, corticoids and kynurenine in a 24-hour urine sample, and turnover of radioactive tryptophan in a second patient with manic depression (adapted from *3*).

psychopathology and physiological and biochemical variables in manic-depressive illness (*2–4*). A second patient also showed increased metabolism of ^{14}C-tryptophan via the kynurenine pathway during depression, when corticoids in the plasma were high (Fig. 2). These findings had been interpreted as indirectly suggestive of a hormonally mediated increase in tryptophan pyrrolase activity (*3*). The restrictions upon this interpretation, for example, the lack of corresponding increases in total 24-hour urine corticoids and kynurenine (Figs. 1 and 2), also had been discussed (*3*).

Mandell and Spooner stated that a report of a hydrocortisone-induced decrease in serotonin in rat brain (*5*) "may be consistent with our demonstration of a steroid-related increase in the breakdown of the indole nucleus through the kynurenine pathway." Richter (*6*), citing a report of increased excretion of xanthurenic acid in the urine in depression as compared to mania (*7*), hypothesized previously that increased metabolism of tryptophan by way of the tryptophan pyrrolase pathway may lead to a reduced formation of indolylamines in depressed patients.

Mandell and Rubin have shown that administration of adrenocorticotropic hormone results in increases in the specific activities of urine kynurenine and indole-3-acetic acid, both of which are products of inducible metabolic pathways (*8*). This finding was interpreted as indicative of some preferential metabolic handling of the administered radioactive tracer. The graph presented by Mandell and Spooner shows a decrease of 5-hydroxyindoleacetic acid (HIAA) radioactivity (disintegrations per minute in a 1-hour sample of urine) on day 2 of tracer study during depression when plasma corticoids were elevated (6 January). Unfortunately the amount of HIAA excreted was not measured in this patient, so that its specific activity cannot be determined. In the absence of information on specific activity, the HIAA radioactivity data presented by Mandell and Spooner do not substantiate Richter's hypothesis, because these data also may have reflected selective handling of the exogenous tryptophan tracer. Furthermore, all these data on urinary excretion permit inferences only about peripheral metabolism of tryptophan, so that the

Table 1. Excretion of 17-hydroxycorticosteroid (17-OHCS) in 24-hour samples of urine from a patient with manic depression (*2*). Results are expressed as means ± S.D.

Period	Days (No.)	17-OHCS (mg/24 hr)
Euthymia	25	4.64 ± 1.60
Mania	11	4.84 ± 1.56
Depression	24	4.75 ± 1.87

metabolic relatedness of peripherally increased activity of tryptophan pyrrolase to decreased serotonin in the brain of patients with depression remains hypothetical. Lapin and Oxenkrug have reviewed this hypothesis in detail (*9*).

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Since we began our program of research directed toward the elucidation of the effects of adrenal glucocorticoids on indole metabolism (*1*), it has been clear that some interesting potential relationships might be established between tryptophan metabolism and steroids in man. Whether, in fact, this would have any ramifications for brain biochemistry seemed in serious doubt, because no brain enzyme has yet been shown to be inducible by adrenal steroids and any peripheral metabolic measures would be markedly dominated by the activity of organs other than the brain (such as the liver and kidney). In our review in *Science*, we

used some work which we did collaboratively with Drs. Clark and Rubin as an example of a research strategy rather than studies of any substantive significance. It is our feeling (*2*) that "induction"-like phenomenon relevant to the brain must involve studies of the brain itself (*3*).

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30 June 1969

Water Generated Earth Vibrations

At Ringwood, New Jersey, the Ringwood Creek passes over a vertical masonry dam, approximately 20 m long by 5 m high, producing a strong beat at flood time (about 10 hz) enough to rattle buildings nearby, and often to be heard plainly a half mile downstream.

According to Rinehart [*Science* **164**, 1513 (1969)] we ought to expect another frequency around 50 hz. Such a note, if present, must however be of low amplitude, too small to be heard above the general din without instrumentation. Apparently a separate explanation is needed for the above-mentioned low-frequency pulses which we plainly see as well as hear.

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Structurally, a dam is quite different from a waterfall. The 10-hz vibration might be associated with the length of the dam rather than with its height.

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22 July 1969

Genetics of Memory

Bovet *et al.* (*1*) have suggested a difference in memory mechanisms between DBA/2J and C3H/HeJ strain mice, based upon a variety of learning paradigms. They observed that DBA/2J mice were superior to the related C3H/HeJ in the acquisition and retention of an active avoidance task, and that they performed differently in a passive avoidance situation. They suggested that their findings supported the notion of a short-term memory peculiar to the C3H/HeJ strain and that the DBA/2J mice have long-term memory storage.

We wish to propose an alternative mechanism whereby these differences can be explained. The C3H/HeJ is one of several strains (including the CBA/J) which exhibits defective vision resulting from a mutation on chromosome XVII. These homozygous recessive *rd* (retinal degeneration) genes are associated with a progressive degeneration of the rods which subserve the function of visual receptors (*2*). Since Bovet *et al.* used light as the conditioned stimulus for the avoidance task, it is not surprising that the C3H/HeJ mice exhibited poorer learning. Both the active and passive tests provided a wealth of visual cues which were probably utilized exclusively by the DBA/2J. The C3H/HeJ mice may have depended upon tactile or temporal cues. They could have shuttled back and forth in the avoidance box at some interval which minimized punishment. Retention of this temporal pattern would probably have been more difficult than retention of a visual conditioned stimulus and could explain the deficits in performance with the longer intersession intervals. In like manner, the visually defective C3H/HeJ mice may not have recognized the passive avoidance device when they were retested after a delay of 45 minutes or more [see figure 9 in (*1*)].

This mechanism may not explain all the differences observed by Bovet *et al.* Other neurological disturbances may accompany the retinal degeneration and provide more direct evidence for their theory. Nonetheless, we feel that an experiment which controls for visual differences should be performed to resolve this question. The shuttle avoidance task performed in complete darkness with an auditory conditioned stimulus should reveal no difference between the two strains if visual cues are the only crucial factors involved. If the results are essentially the same as in their earlier studies, they will have eliminated a confounding variable and strengthened their argument.

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31 January 1969

Concerning the possible role of genetic abnormalities in vision in determining the memory patterns of some C3H sublines (*1*), we have found that comparable levels of avoidance responding were elicited when we adopted auditive stimuli rather than light. The same difference between DBA/2J and C3H/HeJ mice was evident when a delay conditioned stimulus consisting of a 3000-hz tone was adopted in that distribution of practice improved the performance of the former strain while it impaired the performance of the latter (*2*).

Further, comparable levels of transfer were attained when C3H/HeJ mice were shifted from light to tone as from tone to light (*3*).

Further researches conducted with the same strain of mice (C3H/HeJ) demonstrated that it was possible to reach high levels of performance in a five-choice discrimination task when sets of patterns differing by their spatial orientation were adopted (*4*).

With regard to the suggestion of the possible role of temporal cues, the experiments we have designed in order to test this hypothesis have until now brought only negative results.

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