LEARNING, STRESS, AND PSYCHOSOMATIC SYMPTOMS

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Professor Jerzy Konorski was an internationally renowned scientist with a remarkable range of intellectual power and enthusiasm; he also was a warm friend. It is a great honor to be invited to contribute a paper to publications commemorating his life and work.

As infectious diseases are being conquered, other pathological conditions are assuming increasing medical importance. A number of these are strongly influenced by the brain in its central role of regulating a wide variety of vital functions. It has long been believed that the mind affects the body; recent research in supplying objective evidence for an increasing number of such psychosomatic effects. This paper summarizes some experiments from the author’s Laboratory on such effects and also on some of the ways in which amines and hormones in the brain affect behavior. In view of the wide range of Professor Konorski’s interests, it is fitting that the work to be summarized here has been multidisciplinary.

Clinical studies, especially under conditions of combat in war, show that fear and the conflict it can induce can produce a wide range of psychosomatic, neurotic, and even psychotic symptoms. Such work also indicates that purely psychological factors, such as learning when it is dangerous and when it is safe and learning coping responses, can make a great difference in the amount of fear experienced and in its psychosomatic effects (12). However, while clinical observations of human behavior are particularly relevant, it is difficult to untangle confounding factors and thus determine unequivocal causal relationships. The immediately following experiments attempt to fill part of this gap.
Effect of learned discrimination on fear

In one experiment, Dr. Arlo Myers (21) trained thirsty rats to drink in special compartments in which they were restrained so that electrodes could be fastened to their tails. The tails of two rats had these electrodes wired in series so that they received exactly the same strength of electric shock. One member of each pair had a light as a signal preceding the shock so that he could learn the discrimination of when it was dangerous and when it was safe. The other member of each pair did not have any light as a signal so that he could not learn the discrimination. The shock trials were given with the water bottles absent. Then the water bottles were restored and the amount that thirsty rats drank was tested on trials without further shocks. The suppression of drinking (commonly referred to as a conditioned emotional response, abbreviated CER) was used as a measure of fear. During tests with the danger signal off, the animals that had been exposed to signalled and hence predictable shocks drank more water, meaning that they showed less generalized fear than those that had been exposed to unsignalled and hence unpredictable shocks. During tests when the danger signal was on, the situation was slightly reversed. Overall, the animals exposed to predictable shocks drank more water, indicating that they experienced less fear. In these tests the danger signal was off and on for equal times, but in most situations it is off most of the time so that the overall difference will be more strongly in favor of the signalled, predictable condition.

Using a tone, which is more perspicuous to rats than a light, Dr. Jay Weiss (27) has secured results shown in Fig. 1. Although the pairs of

![Fig. 1. The effect of a learned discrimination (possible for the signalled but not for the unsignalled shock) on chronic fear as measured by the amount of stomach lesions. From Weiss (27).](image-url)
rats in different soundproof boxes received exactly the same strength of shocks because their tails were wired in series, those for whom the shock was not signalled had far more stomach lesions than those for whom it was. This study confirms two of the previously-mentioned clinical observations in combat: it shows a striking effect of being able to learn discriminations on the strength of the fear elicited, and it shows that chronic fear can produce an organic symptom, namely, stomach lesions. The value during psychotherapy of teaching a patient to discriminate more accurately between dangerous and safe situations has been pointed out elsewhere (3, 18).

Effect of learned coping response on fear

In experiments on effects of a learned coping response, the electrodes on the tails of two rats again were wired in series. The avoidance-escape rat could perform a simple response, which in one experiment was poking his nose through a hole and in another was rotating a little wheel, in order to turn off the shocks. The yoked rat could perform exactly the same response but it had no effect on the shock. A control rat had electrodes wired on his tail but received no shocks. In a series of experiments, Weiss (28) found that rats that had an opportunity to learn a simple coping response showed much less fear, as measured by the suppression of eating, by plasma corticosterone, or by stomach lesions, than did the yoked controls who received exactly the same shocks but had no coping response. The effect on stomach lesions is shown on the left-hand side of Fig. 2.

One way of interpreting the foregoing results is that, since the cues

![Fig. 2. Being able to learn a simple avoidance coping response to turn off the shock reduces the amount of stomach lesions when the response is simple and the outcome clear-cut, but has the opposite effect of increasing such lesions when the task involves conflict. In both experiments, pairs of avoidance-escape and yoked animals receive exactly the same shock because electrodes on their tails are wired in series. The yoked animals are unable to learn any avoidance response because the manipulandum is connected to the shock control circuit only in the apparatus for avoidance animals. From Weiss (29).](image-url)
produced by the response of performing the successful coping response are never followed by shock, they become the negative cues of a discrimination and hence have a conditioned inhibitory (23) effect on fear. Even performing some fraction of the coping response could theoretically produce some of these cues and hence have a fear-reducing effect. Such a fear-reducing effect of the partial performance of an avoidance response has been described by Miller (11). Weiss (30) has secured evidence supporting this hypothesis by showing that giving the avoidance-escape rats a tone as an additional cue whenever they rotate the wheel far enough to perform the correct response causes them to get even less stomach lesions than rats who did not receive this cue for performing that response.

Conversely, if the conditioned inhibitory value of cues produced by the coping response is weakened by causing that response to deliver a brief shock, so that the rats have to take a shock in order to escape a longer train of shocks, the average length of their stomach lesions is greatly increased (29). This is shown on the right-hand side of Fig. 2. In this condition, instead of having less lesions than their yoked controls, the avoidance-escape rats have many more lesions. This striking reversal is yet another demonstration of the powerful effects of a purely behavioral variable.

**Effect of coping vs. helplessness on brain norepinephrine**

In the foregoing type of stress situation, there is yet another interesting effect of being able to perform a simple, clear-cut, coping response. Three separate experiments (32, 34) have shown that, compared with nonshocked controls, the helpless yoked rats had depressed levels of the neurotransmitter norepinephrine in the brain whereas the rats who received exactly the same shocks but could perform a simple, successful coping response had an increased level of norepinephrine in the brain. One of these experiments controlled for different levels of activity by having the coping response for one group be freezing and not moving and for another be running. These results are especially interesting because the drugs that are useful in treating some, but unfortunately not all, cases of depression are those that increase the effectiveness of norepinephrine (and possibly other biogenic amines) at the synapse, and the drugs that have the opposite effect of reducing the effect of norepinephrine (and possibly other biogenic amines) at the synapse also have the opposite effect of causing or intensifying depression if they are given to the wrong patient. Schildkraut (25) has advanced the hypothesis that situationally-produced depressions may involve the same reduction in the effectiveness of norepinephrine at the synapse. The foregoing experiments provide evidence that a hopeless situation does indeed produce a reduction
in the norepinephrine level of the brain, which presumably will decrease its effectiveness at the synapse. Perhaps this is a normal mechanism for producing a mildly depressed mood, which often is adaptive in preventing the organism from wasting too much energy by struggling with a hopeless situation. But perhaps when this mechanism is intensified by either a biochemical error or an extraordinarily hopeless experimental situation, it may lead to a maladaptive level of depression which in turn may create further failure, thus producing a vicious circle of reduced norepinephrine level and continued depression.

Conversely, the increased level of norepinephrine in the animals that can perform a coping response may be a normal mechanism for producing an elevation of mood that helps to keep successful responses going at a high level. This increased level of norepinephrine suggests a positive mental-health value from meeting and successfully overcoming difficulties.

Role of brain amines in depressive after-effects of stress

The vicious circle hypothesis described above assumes that a stress-produced depletion in norepinephrine will have a depressive effect on behavior. In order to secure further evidence on this point, a series of experiments was performed on rats subjected to the severe stress of unpredictable, inescapable electric shocks and/or the stress of swimming in cold water. These experiments showed that the foregoing stresses produced a depression of norepinephrine in the brain (6) and a transient depression in the ability to learn and perform shuttle avoidance in a situation involving the effort of crossing a barrier (31). The same study showed that this after-effect was not a general interference with learning since the rats could learn a much less effortful avoidance response. In the more effortful situation involving the barrier, the rats were physically able to perform this response but did not seem to be able to muster the psychological activation to perform it. That a depletion of norepinephrine (and possibly other biogenic amines) was involved in this deficiency was shown by the fact that it could be prevented by an injection of pargyline, a drug that helps to prevent the depletion of these amines, and could be very closely mimicked by the effects of an injection of tetrabenazine, a drug that has the opposite effect of depleting these amines (6). Neither of these effects would be expected from the learned helplessness hypothesis advanced by Overmier and Seligman (22) and Seligman and Maier (26) 1.

1 That something like learned helplessness or its opposite can indeed occur has been discussed theoretically by Dollard and Miller (3, p. 132–133) and studied experimentally (5, 13).
Effects of habituation to stress on enzyme induction and on behavioral resistance to stress

The depletion of a neurotransmitter, such as norepinephrine, removes the process of synthesis from inhibition by its end-product, and this induces an increase in the activity of the enzyme that synthesizes it. From this phenomenon we might expect that rats which were exposed to similar strong, inescapable shocks on each day for a series of days would increase their capacity to synthesize norepinephrine and hence would suffer less depletion after one of the later exposures. Then if the depletion produced by the strong shocks is indeed the primary factor in the behavioral deficit, they should show less such deficit.

Experiments were performed to test this hypothesis (33). Rats that were exposed to severe shocks each day for 14 days and then tested after severe shocks on the 15th day showed a higher level of activity in the enzyme tyrosine hydroxylase, which synthesizes norepinephrine, than did rats that received the shocks for the first time on the 15th day. As would be expected from this increased synthesis, the previously shocked rats showed much less depletion of norepinephrine than those that had not been previously exposed. But this was not the only effect. Norepinephrine is removed from activity at the synapse by a re-uptake mechanism. After the shocks on the 15th day, the rate of re-uptake of norepinephrine was reduced in the rats that had had previous exposure compared with that of the rats that had not been previously exposed to shock. Both this reduction in re-uptake and the lessened depletion would be expected to have the same effect of making norepinephrine more effective at the synapse, and hence, if our hypothesis is correct, making the behavior of the previously exposed rats more normal than that of the ones that were shocked for the first time. And, in fact, the behavioral tests bore out this prediction. Whereas the rats receiving the strong unavoidable shocks for the first time failed to learn in immediately subsequent tests in the different shuttle-avoidance apparatus, those that had received shocks on the preceding 14 days showed normal avoidance learning.

As an additional pertinent fact, not related to the norepinephrine story, the previous habituation to shock also considerably reduced the degree to which the test shocks elevated the level of plasma corticosterone.

Finally, if the foregoing beneficial effects of prior habituation to electric shocks were indeed a function of the depletion of norepinephrine, rather than from some other more general effects of the daily stress, exposing the animal to 14 prior depletions induced by a drug should have similar beneficial effects on the rat's behavior after severe shocks. This was-
tested by using tetrabenazine, a drug that produces a rapid but transient depletion of norepinephrine and also of other monoamines. This prediction was indeed confirmed. One group of rats which were exposed to daily injections of tetrabenazine for 14 days were protected from the disruptive after-effects on avoidance learning of an injection of tetrabenazine on the 15th day; another similarly treated group was equally protected from the after-effects of severe electric shocks given for the first time on the 15th day. The results of this test are shown in Fig. 3. From the

![Graph showing latency to respond from CS onset](image)

Fig. 3. Prior exposure to a norepinephrine-depleting drug, tetrabenazine, "toughens up" the rats so that they are able to learn the avoidance task immediately after exposure either to that drug or to traumatic electric shocks. From Weiss et al. (33).

top two curves it can be seen that, for the rats which received only placebo injections for the first 14 days, there is a complete failure to show avoidance learning, as indicated by the long latencies that fail to decrease during successive trials of the avoidance task. By contrast, good avoidance learning, as indicated by low and progressively decreasing latencies, is shown by the groups that had been toughened up by 14 days of injections of tetrabenazine before receiving on the 15th day either one more injection of the drug or severe electric shock. Both of these groups performed as well as the control group that received only placebo injections throughout. These results support the conclusion that both the depressive after-effects of the severe electric shocks and the toughening-up effects of prior exposure to such shocks are mediated by the reduc-
Fig. 4. Differential uptake of radioactively tagged corticosterone by pyramidal cells in the hippocampus. The dark bands show the pronounced localization of the uptake. From McEwen et al. (8).
tion in the brain level of norepinephrine (and perhaps also other monoamines) that is produced by these severe, unpredictable, unavoidable electric shocks.

The brain as a target organ for corticosterone

The experiments described earlier in this article, and a great many others from other laboratories, have shown that when the animal is under stress the adrenal glands release more corticosterone into the blood. For this reason, Dr. Bruce McEwen and his colleagues (8) were interested in where corticosterone goes in the brain. By injecting labelled corticosterone into the adrenalectomized rat, they secured the results shown in Fig. 4. It can be seen that the dark silver grains indicating radioactivity from the corticosterone are concentrated primarily over a layer of pyramidal cells in the hippocampus. Other regions of the brain, including the pyramidal cells of the cortex, were not strongly labelled. Examination under greater magnification showed that the radioactivity was located primarily in the nuclei of these cells. Other tests showed that the binding there involved a limited-capacity uptake mechanism. Work on more easily studied peripheral organs in other laboratories has shown that this type of uptake by the nuclei of cells is characteristic of the target organs of hormones and that the hormone acts in the nucleus by derepressing genetic information there that controls the synthesis of proteins such as those that function as enzymes. These proteins in turn affect the metabolic activity of the cells.

Following up the earlier indications of such localization by Dr. McEwen's group, Pfaff, Silva, and Weiss (24) used telemetry techniques to record from single neurons in a region of the hippocampus showing high uptake of corticosterone. The rats were hypophysectomized in order to avoid interference from endogenous hormones. These investigators secured the results shown in Fig. 5, from which it is clear that the corticosterone produced a decrease in the firing of these hippocampal neurons. The hormone did not produce similar decreases in the firing of neurons in the cortex where there had been no evidence of selective uptake of this hormone. This pilot study gives a strong indication that corticosterone has the specific effect of inhibiting the firing of the cells in the hippocampus that have special affinity for its uptake.

It is known that lesions in the hippocampus (which completely eliminate the firing of these neurons) have the effect of causing animals to continue to go to a place where they no longer find food, or, in other words, of increasing their resistance to experimental extinction. Therefore, Dr. David Micco (unpublished work) decided to study the effect of corticosterone on the resistance to experimental extinction. He found
Fig. 5. Inhibition of single-unit activity in the hippocampus by corticosterone injected i. p. in 0.05 ml ethanol as a vehicle. One-second samples from the record show unit activity before (left) and after (right) injection of corticosterone. From Pfaff et al. (24).

Fig. 6. Differences in uptake of dexamethasone and corticosterone in the hippocampus and in the anterior pituitary. From de Kloet et al. (7).

Fig. 7. Effects of removal of corticosterone by adrenalectomy (ADX) and of restoration therapy by dexamethasone or by corticosterone on the speed of running during acquisition and experimental extinction. The related hormones have the differential effect on extinction that would be predicted from the differential uptake in the hippocampus shown in Fig. 6. (From unpublished work by Dr. David Micco.)
that this hormone does indeed increase the resistance to experimental extinction.

Since the initial localization studies, de Kloet, Wallach, and McEwen (7) have found that, as Fig. 6 shows, whereas the natural hormone corticosterone goes primarily to the hippocampus and also somewhat to the pituitary, the related synthetic hormone dexamethasone goes primarily to the pituitary with very little to the hippocampus. The uptake of dexamethasone by the pituitary fits in with its clinical usefulness in suppressing the secretion there of ACTH, where its effects are similar to but considerably stronger than those of corticosterone. The fact that it has these effects but does not go to the hippocampus makes it useful as a control for possible effects of corticosterone on the pituitary and for any general (e.g., peripheral) effects of this type of hormone.

The results of an experiment by Dr. Micco utilizing this control are summarized in Fig. 7. The left-hand set of columns shows that none of the treatments had any appreciable differential effect on acquisition. The right-hand set of columns represents the results during the first trials of experimental extinction. Comparison of the normal animals represented in the first column with the adrenalectomized (ADX) ones in the last column shows that the elimination of all corticosterone by adrenalectomy has had the effect of speeding up the process of experimental extinction and hence producing slower running. This effect would be predicted from the release of the hippocampus from partial inhibition by corticosterone, i.e., an action opposite to that of a lesion. In the next to the last column it can be seen that replacement therapy by dexamethasone, which would not be expected to have any effect because it does not go to the hippocampus, indeed does not change the behavior toward normal. By contrast, replacement therapy with corticosterone, which does go to the hippocampus, does restore the behavior to normal. Thus the difference in the behavioral effects of these two closely related hormones is exactly what would be expected from the difference in their uptake in the hippocampus.

The picture would be rounded out nicely if subsequent work demonstrates that corticosterone and dexamethasone are differentiated also in their effects on the firing of pyramidal cells in the hippocampus.

Fear as a learnable drive motivating the learning of new responses

A large amount of much earlier work from this laboratory has shown that fear can be learned as a new response to a previously neutral stimulus stimulation and then can serve as a drive to motivate the learning and performance of a new responses in the same general way that hunger, thirst, and other drives do; furthermore, a prompt reduction in fear can
serve as a reward to reinforce trial-and-error learning or, in other words, Type II conditioning (2, 10, 11). Fear can motivate the learning and performance of adaptive behavior, such as buying insurance or driving more carefully. It also can produce conflicts (9, 12, 14). Fear plays an important role in the production of neurotic behavior; therefore, the elimination of unrealistic fears is an important aspect of psychotherapy (3). Drugs such as alcohol and barbiturates specifically reduce the strength of fear (15, 16) and, as would be expected from this fact, when the animal is frightened the administration of such drugs can serve to reward the behavior that secures the dose of the drug (1).

Previously it was thought that Type II conditioning, also called trial-and-error learning, instrumental learning, or operant conditioning, was limited to the skeletal muscles mediated by the somatic nervous system. Recently, evidence has been accumulating that in one way or another visceral responses mediated by the autonomic nervous system also can be affected by such learning. The problem of investigating such visceral learning has turned out to be unusually difficult and treacherous. There have been difficulties in replicating the earlier experiments on rats paralyzed by curare (4, 17, 19). On the other hand, there have been some successes (20). There is reason to believe that either direct or mediated learning of visceral responses may play a role in the etiology and therapy of some psychosomatic symptoms.

The medical implications of the extensive work referred to in this sub-section have been summarized in more detail elsewhere (18).

Brain cells that fire to fear

In determining the detailed role of fear in the learning of new responses and in studying the interactions between fear and conflict that are relevant for psychiatry, one of the difficulties has been the lack of an independent moment-to-moment measure of fear (11). Recently, however, Vertes and Miller (35) have discovered in the freely moving rat large cells in the region of the nucleus reticularis pontis caudalis that will respond to a conditioned stimulus (CS) for electric shock but not to the arousal produced by a CS for the delivery of water to an extremely thirsty rat. The firing of these cells is not affected by whether the rat responds to the danger signal by active movement or by the opposite response of "freezing"; these cells differ also in other ways from those cells that respond to specific movements.

Figure 8 shows a record of the responses of one of the cells that respond specifically to a conditioned stimulus for electric shock. Each pair of strips is the continuous record of an entire trial. The top two strips (A) show the large and sustained increase in firing to a tone that is a condi-
tioned stimulus for electric shock. The next pair (B) show little or no sustained increase in firing to a light that is a CS for water under the motivation of severe thirst. C shows approximately the same sporadic low rate of baseline firing (it should be remembered that the rat is in an apparatus in which he has received many electric shocks) to a clicker that is used as a neutral stimulus. D shows the greatly increased firing to this same clicker after it has been paired with electric shock for a few trials.

Fig. 8. Differential response of a neuron in the reticular formation of the rat to: A, tone as a conditioned stimulus (CS) for electric shock; B, light as a CS for water; C, clicks as a neutral stimulus; and D, the same clicks after pairing with shock. Each pair of traces is a continuous strip of an entire test trial. From Vertes and Miller (35).

Ten cells of the foregoing type were first informally identified and then formally tested. In the formal tests for each one of the 10 cells, the response to the CS for the electric shock (a different stimulus for different animals) was reliably greater ($P<0.001$ in each case) than the response to either the CS for water or the neutral CS. It is hoped that
the subsequent study of the firing of such cells during various conditions of avoidance learning and conflict behavior will show that such firing can be employed as a useful index of fear. Perhaps such a neurophysiological index may help in the further analysis of the phenomena described in this paper. Tracing the anatomical connections of these cells, which are in a region where giant cells have long ascending and descending processes with many connections, may illuminate also some of the neurophysiological mechanisms involved in fear and/or conditioned arousal.

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