THE PHYSIOLOGICAL BASIS OF MEMORY[1] 131

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The present review confines itself to recent developments in the physiological bases of memory. The review deals mainly with advances produced by the application of techniques which cause amnesia. There is also a section on experiments using spreading depression as a tool. An attempt has been made to evaluate these topics critically and in depth.

Protein Synthesis Inhibition and Memory

The original impetus to the work with protein synthesis inhibitors was the idea that memory storage was in some way connected with the synthesis of protein molecules. If this was the case, it should be possible to prevent the formation or maintenance of memory after a learning experience by the administration of substances preventing the synthesis of protein. Flexner, one of the earliest and most thorough investigators using this technique, has recently published a valuable review of his work (31).

Flexner and his collaborators teach mice what is essentially an escape task in a Y-maze. After the mice are trained, puromycin is injected intracerebrally 1 to 60 days after training. The mice are typically retested 3 to 4 days after treatment. Memory loss is expressed in terms of a percentage savings score. "These percentages are calculated by subtracting the number of trials or errors to criterion in the retention tests from the number to criterion in training, dividing by the number in training and multiplying by 100" (31). Such a score could produce a serious overestimate of the amount of amnesia if the rate of learning is slowed down by the drug. Unless there is an independent estimate through the use of preinjected controls of the effect of the drug on the rate of learning, the number of trials to criterion during retest does not specify the relative contributions to the total relearning score made by amnesia and by altered rate of learning. Flexner et al. (31) state about puromycin-treated mice, "some reach criterion on second learning in practically the same number of trials with the same number of errors as on first learning; in others, second learning is substantially more difficult than first learning." There is, therefore, reason to believe that rate of relearning was affected in this set of experiments. Given this measure then, it is possible that in these experiments a trivial degree of

[1] The survey of literature pertaining to this review was concluded in May 1968.

forgetting would look like a complete amnesia if on retest the mouse learned very slowly.

Flexner et al. (31) infer that the memory trace spreads as it becomes older. Mice injected one day after training with 90 μg of puromycin, using injection into the temporal region of the brain, lose their memory of the habit. On the other hand, with an interval of 11 days between training and injection, injection into the temporal region appears no longer sufficient to cause amnesia. The dose has to be distributed into at least three sites (temporal, ventricular, and frontal) bilaterally symmetrical. This is taken to be evidence of the spread of the memory trace with time after learning. However, there are alternative conclusions that can be drawn. No preinjected controls are ever run. Consequently, we do not know whether the widely injected mice are more impaired in their capacity to learn than their counterparts injected only in the temporal region. Further, the difference obtained may be attributed to effective dose rather than spread of the memory trace. We could suppose that the memory trace is scattered over a large number of sites and that soon after learning the memory substrate is sensitive to a lower level of drug. It has been shown that an injection of puromycin into the temporal cortex produces only low protein synthesis inhibition in all other sampled areas of the brain (31). This low effect might therefore be sufficient to block memory initially. However, a combined set of injections (temporal, ventricular, and frontal) causes a very much higher puromycin inhibition of protein synthesis in other areas besides the temporal. Thus while a temporal injection may no longer cause amnesia because the traces in other sites require a larger depression to be blocked, this can be achieved by a different spatial distribution of the injection.

Subsequent to these results with puromycin which support the idea that protein synthesis is necessary for the formation and maintenance of memory, Flexner & Flexner (29) have reported that intracerebral injections of small quantities of saline at various times after puromycin treatment abolished the puromycin-induced amnesia. It therefore seems that puromycin simply blocked retrieval in some way and that the memory trace itself was in fact unimpaired by puromycin. In this experiment, puromycin injections were made one day after training, with the exception of subsidiary groups where injection was made after a longer interval. Saline was then injected at intervals varying between 4 hr and 60 days.

It could be argued that Flexner's experiments have a bearing on the maintenance of memory but not on its formation because they have only made injections one day or more after training. Barondes & Cohen (5) trained mice in a situation similar to Flexner's, either in the presence of puromycin or with puromycin injected immediately after learning. They found in both cases that memory was present for 45 min after training but was almost lost after 3 hr. Therefore, puromycin also seems to have an effect on the formation of memory. Flexner & Flexner (30) attempted to discover whether this effect of puromycin on presumed memory formation

was also reversible by saline injection. They found that "in the presence of puromycin, our mice, when naive to the maze, are exceptionally difficult to train." They were compelled then to use a training schedule which makes the mice trained in such a manner difficult to compare with other groups. However, a second group injected with puromycin immediately after training can be compared. Flexner & Flexner (30) summarize the results of their studies with puromycin followed by saline as follows:

> It was shown that puromycin administered to mice one or more days after maze-learning blocks expression of memory; the blockage can be removed by intracerebral injections of saline. We present evidence that intracerebral injections of saline are relatively ineffective in restoring memory when puromycin is administered either before or immediately after training; in these two situations puromycin appears to interfere with consolidation of memory.

Such an important conclusion should be examined further. We shall consider only the group injected after training, as it is the only one which is comparable to other groups which have been run. This group was trained, injected with puromycin immediately upon being trained, injected with saline 5 days later, and then retested 10 days after original training. The difference in retention between the mice treated with saline and those treated only with puromycin was clearly significant.

Injection of saline seems therefore to reverse the amnesia produced by puromycin injected immediately after training. The question is then asked whether such a reversal is as effective as when saline is injected into animals treated with puromycin one day after training. Flexner & Flexner (30) answer their question as follows:

> Our earlier results on the efficacy of saline in restoring memory after treatment with puromycin referred to 47 mice in which puromycin was given one or more days after training and followed 30 hr to 60 days later by intracerebral injections of saline. . . . These savings are marginally significantly greater ($p<.05$) than those obtained when puromycin, given immediately after training, was followed 5 days later by saline (p. 311).

It is doubtful if the group of 47 animals mentioned is in fact a proper control group, because it differs in other ways besides the time after training when puromycin was injected.

One of these differences which seems important concerns the time between the puromycin and saline injections. Inspection of Table II in the previous experiment (29) describing this group shows that there seems to be an interaction between time between puromycin injection and saline injection and subsequent recovery from amnesia. For instance, when the interval is 30 hr, no mice lose their memory, one has impaired memory, and 7 retain their memory. On the other hand, when the intervals between puromycin and saline injections are from 2 to 12 days, one animal loses its memory, 9 have impaired memory, and 13 retain their memory. Both the 30-hr group and the 2-to-12-day group were injected with puromycin at the same time

after training and were used as a part of the same baseline comparison group of 47 mice. Yet the probability that the 30-hr and 2-to-12-day groups are different is greater than the probability that the 2-to-12-day group and the group injected with puromycin immediately after training are different. (I thank Dr. P. H. Lindsay for calculating this from the published data.)

The marginal difference between the mice injected with puromycin immediately after training and those injected one day later could therefore be due to the fact that they were also injected with saline at different times after puromycin. Furthermore, the group of 47 mice injected at least 1 day after training, used as a baseline of comparison of the mice injected immediately after training and with saline 5 days later, is also heterogeneous in another way. One subgroup was given 6 intracerebral injections of puromycin 13 to 15 days after training. The *N*s in each group are quite unequal, so that the total baseline becomes almost completely arbitrary. Therefore, it cannot be concluded safely that saline is relatively less effective in restoring memory when puromycin has been administered immediately after learning. Thus the experiments suggesting reversal of puromycin amnesia with saline should be examined with caution when it is claimed that memory storage rather than retrieval has been affected by a treatment.

Flexner et al. (31) also report that acetoxycycloheximide, an extremely potent protein synthesis inhibitor, does not have an amnesic effect when injected one day or more after training. However, when acetoxycycloheximide is injected in mixture with puromycin, it protects against the amnesic effects of puromycin. Flexner et al. (31) attempt to explain this in terms of the ways in which the two drugs inhibit protein synthesis. On the other hand, it has never been demonstrated that puromycin or any other protein synthesis inhibitor has its action on memory through a direct effect on protein synthesis rather than through some indirect or side effect. Koenig (36), for instance, has shown that puromycin depresses cholinesterase synthesis and that actinomycin-D has the opposite effect (37). Puromycin blocks the increase of acetylcholinesterase by actinomycin-D. Dahl and Leibowitz, together with the reviewer (quoted in 21), have shown a remarkable similarity in the time course of amnesic effect between puromycin and anticholinesterases.

Barondes & Cohen (6) have reported recently that subcutaneous injection of 240 μg of acetoxycycloheximide in mice 5 min to 5 hr before training in a T-maze produces amnesia for the habit. The mice were trained to a criterion of 5 out of 6 correct. This result is in marked contrast with previously reported results by these workers (15), where intracerebral injections of the same substance which produced at least as high protein synthesis inhibition at the time of training were without effect on a well trained habit. (However, an amnesic effect on a habit learned to a criterion of 3 out of 4 correct was observed.) Barondes & Cohen (6) also found that memory was unimpaired at 3 hr, although amnesia set in 6 hr after training. From this it is argued "that a different process is utilized for memory storage during this

period and that the absence of a long-term process, which is apparently dependent on cerebral protein synthesis, does not become manifest until the short-term process has decayed sufficiently" (6).

The inadequacy of such an argument to establish different memory processes is best shown by quoting from Flexner et al. (31): "In mice trained to criterion both recent and longer-term memory are maintained for 10 to 20 hr after injection of puromycin, then they disappear permanently." From such evidence it can be argued more plausibly that it takes some time for a single process to become irretrievable. Though belief in different stages and processes in memory has become popular, the fact is that no one has devised an experiment capable of deciding between a single process and a multiple process theory.

Another group of studies on amnesia and protein synthesis inhibition has been performed by Agranoff and his associates. Goldfish are taught to avoid shock in a shuttle-box apparatus. They are given a fixed number of trials, at the end of which only a little learning has occurred. Treatment is given either before or soon after training, and retesting is done at different times after training. Agranoff & Klinger (3) have found that injection with puromycin immediately after training causes goldfish to forget after 3 days. Potts & Bitterman (47) added an element of discrimination to the shuttle-box situation used by Agranoff. Instead of using a white light as a warning stimulus, the goldfish could discriminate what color light was followed by shock. They trained the goldfish giving 20 trials a day on 6 training days one week apart. Each set of trials was followed by an injection of 170 μg of puromycin intracranially. The results show that the puromycin-injected goldfish learned to avoid though at a slower rate than the controls. However, it seems that the relative efficiency of discrimination (given different baselines of responding) was about the same for the experimental as for the control fish. Potts & Bitterman (47) suggest that puromycin does not interfere with the consolidation of memory in general but with the consolidation of conditioned fear.

An alternative explanation may be suggested. As the ECS experiment of Schneider & Sherman (59) indicates, the effect may be due to an obliteration or diminution of fear by an interaction between fear arousal and treatment when these are temporally contiguous. Memory consolidation may not be involved in the puromycin effect at all.

That the effect of puromycin resembles that of ECS extremely closely in the parameters of retrograde amnesia it produces in goldfish has been shown by Davis, Bright & Agranoff (19). Agranoff et al. (2) report that actinomycin-D injected intracranially immediately after learning produces partial amnesia. An injection of the drug 3 hr after training does not produce amnesia. A similar effect is reported with injections of acetoxycycloheximide. It is not reported how long memory persists after the injection. The authors state: "Since protein synthesis is not significantly inhibited for several hours after the injection of actinomycin-D, we suggest that this drug impairs memory not by blocking protein synthesis but by some other means, pre-

sumably by its well-known role in blocking DNA-mediated RNA synthesis."

Agranoff has recently reported (1) that intracranial injections of 6 per cent KCl into the goldfish produce retrograde amnesia for 12 to 18 hr, a much longer time span than affected by protein synthesis inhibitors. Memory apparently also takes 12 to 18 hr to disappear after treatment. There is no suggestion that such disappearance of memory after treatment is more rapid with any of these agents the longer the interval between training and drug treatment. However, this is what we would expect if the two-stage theory were correct. The persistence of memory after treatment is attributed to a decaying short-term memory process. The later in the life of this process treatment to knock out the long-term memory is given, the shorter the time over which memory should be observed. A single-stage model would predict the opposite, if anything.

Davis (17) has reported further on his previously described evidence (18) for an environmental trigger to memory fixation in the goldfish. It has been shown (see above) that puromycin has gradually less effect the longer after the learning experience it is injected. Davis reports that if the goldfish is left in the training environment after training, the time is extended during which the memory is vulnerable to puromycin. Davis interprets this to mean that memory fixation is suppressed by conditions in the training environment. This conclusion must be accepted with caution. It can be seen from Davis' data that uninjected controls show a memory deficit which rapidly increases with the time they are left in the training environment. Such a deficit does not occur if such controls are returned to their home tanks. It can be argued then that puromycin injections, given to fish that have been left in the training environment for increasing times, are acting on a rapidly decreasing memory substrate as indicated by a behavioral impairment of memory. For instance, a puromycin injection made immediately after training affects a memory where the normal retention index 72 hr later would be $-.38$. The same injection made 3.5 hr after training affects a memory where the normal retention index would be -1.22, significantly different from the case where the goldfish is removed immediately from the training environment. After 24 hr in the training environment, retention deficits of controls are very large and not significantly different from deficits shown by the groups which received puromycin after 24 hr in the same environment. It is possible that a weaker memory remains susceptible to puromycin for a longer time than a stronger one, and Davis has not excluded this possibility. Until the nature of the decrement observed in untreated fish kept in the training environment is clarified, the fact that puromycin remains an effective agent for longer after training when fish are kept in the training environment can hardly be taken as evidence for an environmental trigger of memory fixation. Another possible explanation of the result is that puromycin, like ECS in Schneider & Sherman's experiment (59), is effective while the animal is in a state of fear. Such fear would be sustained by the training environment. Potts & Bitterman (47) have criticized the environmental trigger explanation by

showing that goldfish trained to a much higher criterion do not suffer from amnesia even though injected immediately upon being taken out of the training environment. This exposure to the training environment should on Davis' argument have postponed fixation, thus rendering the memory vulnerable to puromycin. However, this experiment of Potts & Bitterman does show that memory strength is an important variable in susceptibility to puromycin.

The work with protein synthesis inhibitors seems to face major unsolved problems. Flexner's work with puromycin indicates that the effect is not on memory storage but on retrieval. The question must be asked whether such is not the effect of other protein synthesis inhibitors also. A more severe problem is posed for the protein synthesis inhibitors shown to be effective only when they are administered close to learning. It must be shown that they affect memory at all, let alone whether they affect retrieval or storage. The possibility of an interaction between motivational effects and drug treatment remains open, especially in view of recent results with ECS. Even if a real effect on memory is substantiated, there remains the question whether such an effect is due directly to protein synthesis inhibition or to some indirect or side effect of the drug.

Cholinergic Drugs and Memory

A series of experiments has shown that cholinergic agents can alter recall in various ways (20). In the initial experiment, DFP (diisopropyl fluorophosphate) was injected intracerebrally various times after training. Rats had been trained to escape a shock by running to the lit arm of a Y-maze. Retest was always conducted the same time after injection. In this way any differences found in recall could not be due to differences in effective drug dosage at time of testing. It was found that there was a small degree of amnesia when injection was made half an hour after training. At 3 days after training, the drug had no effect. On the other hand, there was considerable amnesia at 7 and 14 days after training. A very similar time course was obtained with intraperitoneal injections of physostigmine (22). Both DFP and physostigmine are anticholinesterases. Therefore, they slow down the destruction of acetylcholine by combining with cholinesterase. At low levels of synaptic conductance, such drugs will facilitate transmission by preventing the destruction of acetylcholine and thus aiding the depolarization of the postsynaptic membrane. At high levels of synaptic conductance, synaptic transmission is blocked because of the accumulation of acetylcholine. It was therefore concluded that with the exception of a short time after initial learning, the conductance of a synapse increased with time after training. In this way an anticholinesterase would have no effect soon after learning but would cause a block as synaptic conductance improved with time. To test this, parallel experiments were performed with scopolamine, an anticholinergic agent. Such a drug diminishes the effective amount of acetylcholine. It would therefore be expected that this drug would have its

maximum effect on memory when anticholinesterases had no effect (when conductance was low) but would have no effect when anticholinesterases blocked memory. That this is the case was verified in two experiments. In the first (25), exactly the same escape habit was used as in the experiments with anticholinesterases. In the second (61), an appetitive habit was employed, and both DFP and scopolamine were used within the same experimental design. The results were very similar to those obtained with the escape habit. The effects of the injection of DFP were also tested when the escape and appetitive habits were almost forgotten (23, 61). Rats injected with a control injection 28 days after training had almost forgotten the escape habit. However, when injected with DFP at this time, they showed almost complete retention. A similar facilitation was obtained with the almost forgotten appetitive habit when it was 21 days old. Forgetting in the case of the appetitive habit was faster. The dose of DFP producing facilitation of an almost forgotten habit is the same as that which blocks the recall of the same habit when it normally is well remembered. These results suggest that forgetting is due to a lowering of synaptic conductance, because anticholinesterases facilitate synaptic transmission where synaptic conductance is low.

While the drug data suggested that there was an increase in the substrate of memory between 3 and 7 days after training, no improvement in the performance of undrugged controls was detected from 3 to 7 days after training. In other words, anticholinesterase has two different effects on memory, no block at 3 days and a block at 7. However, habits were as well performed after 3 days as they were after 7. This could have been due to a "ceiling" effect, as the rats had been trained to a high criterion and therefore could show no behavioral evidence of improvement from 3 days to a week because their performance was almost perfect. Consequently, rats were undertrained (34) and retention measured at various times after training. Retention without any injection was much better at 7 or 10 days than at 1 or 3 days. This confirmed the inference made from the drug studies.

It has also been found (22, 23) that the amnesic effect due to DFP is temporary. This agrees with the idea that the amnesia is due to synaptic block. Amnesia should only be observed in the presence of sufficient quantities of anticholinesterase when excessive acetylcholine is present. A way of diminishing the pile-up of acetylcholine when anticholinesterase is present is to give the rat longer pauses between trials during retest. This is because, with the rate of destruction of acetylcholine slowed down by phosostigmine, it takes longer for an excessive or blocking amount of acetylcholine to be cleared away. Under physostigmine, when trials during retest are spaced (50) there is almost no amnesia, though amnesia is severe when trials are massed. On the other hand, reversal learning under physostigmine is easier when trials are massed than when they are spaced. Reversal is easier when there is no memory of the original habit.

An interaction has been found between the degree of original training

and the effects of anticholinesterase on memory (24). Weakly learned habits are strongly facilitated, whereas well learned habits are blocked by the same dose of DFP. The drug has no effect on habits learned to an intermediate degree. This relationship has been demonstrated by varying the number of trials given on the same task. The same relation holds if instead of varying the number of trials on the same task we hold number of trials constant but vary task difficulty. The easier task is then better learned than the difficult task at the end of the same number of trials (40). Difficulty was increased by dimming the light to be discriminated. DFP produced memory block with the easy task, whereas it caused strong facilitation with the difficult task. Again exactly the same dose of drug was used to produce these opposite effects. These results suggest that conductance in a set of synapses increases with degree of training.

As has been stated above, it is possible with anticholinesterase injections to produce amnesia for 7-day-old habits while leaving the memory for 3-day-old habits unblocked. This property has been utilized to analyze the nature of extinction (26). If extinction is a separate habit, it should be possible to leave it intact, so that it should be remembered on retest while the original habit is unavailable. A rat in this condition should therefore find it much more difficult to relearn the original habit on retest than preinjected control rats, or rats which were extinguished soon after learning. In the rats extinguished soon after learning, both the memory of original learning and of extinction should be blocked. To test these predictions, rats were trained to approach a light for a reward of sugar-water in a modified Y-maze 7 days before an injection of physostigmine. Then at various times after initial training they were placed in the maze and not rewarded for approaching the light, until a criterion of nonresponding was reached. The rats which were extinguished 3 days before injection took almost twice the number of trials to relearn on retest when compared with controls and rats extinguished 6 days before injection. On the other hand, they learned a reversal of the original habit more quickly than such control groups. This suggests that during extinction a separate habit is learned which opposes the performance of the initially rewarded habit. From the results on reversal it seems plausible that such an opposing habit is an aversion to the initially rewarding stumuli. This supports the theory of extinction put forward by Miller & Stevenson (43).

Interhemispheric Transfer of Memory

A very large number of experiments have now been carried out to study characteristics of the memory process by means of spreading depression since Bureš (9) first used such a technique for this purpose. The technique of spreading depression can selectively abolish most neural activity in the cortex covering one hemisphere of a rat. Such an inactivation is reversible. In an initial set of experiments, rats were trained with, say, the left half of the cortex depressed, and then tested with only the right side depressed. If the

rats could not perform the original habit, it was concluded that the memory trace had been stored in the originally nondepressed hemisphere. When this hemisphere was depressed during test, the stored memory was unavailable. In a second generation of experiments, the characteristics of the transfer of a memory trace from hemisphere to hemisphere were studied. It was found that if the animal was given the opportunity to make one or two rewarded responses with neither hemisphere depressed, after it had been trained with one hemisphere depressed and before it was tested with the other hemisphere depressed, it performed well during test. This was interpreted to mean that the trials when neither hemisphere was depressed enabled the memory trace to move from the educated hemisphere to the ignorant one.

In a further refinement, an attempt was made to measure the time necessary for transmission to take place from the trained hemisphere to the untrained after the trial with both hemispheres undepressed. This was done by producing spreading depression in the previously trained hemisphere at various times after the trial with both hemispheres undepressed. It was found that the degree of transfer decreased as the time between the trial with both hemispheres undepressed and the subsequent depression of the originally trained hemisphere were brought closer together. A similar attempt was made to measure how long it would take the receiving hemisphere (i e., the originally depressed and so untrained half) to consolidate the memory trace transmitted to it by the trained hemisphere. For this purpose experimenters varied the interval between the first time one hemisphere was depressed and its subsequent depression. As spreading depression can also produce retrograde amnesia, it was thought that the period during which the transferred trace was vulnerable to spreading depression would give a measure of the time that the trace took to consolidate.

While such experiments have been elegant and their interpretation in terms of the anatomy of memory enticing, difficulties have begun to appear. Some habits appeared not to be confined to one hemisphere, and so a subcortical locus of storage had to be posited (10). Even more perplexing is the finding that rats trained to go, say, to the left when one hemisphere is depressed, go right when the other hemisphere is depressed (49 a, b). While it is true that the rats did not perform the original habit of going left when spreading depression was shifted to the other hemisphere, it is somewhat surprising that their behavior deviated from random performance to the same extent as before the hemispheres were switched. While this was claimed as a loss of the learned habit, it could equally well be interpreted as an acquisition of the mirror image habit by some mysterious means. However, a simpler explanation is that the rats during initial training had learned by orienting themselves with respect to the lateralized symptoms to which unilateral spreading depression gives rise. Then when the side of the cortex which is depressed is switched, the rats will perform the mirror-image habit. No forgetting has taken place.

Such considerations prompted Schneider (53) to reinterpret the results

obtained with the use of spreading depression. As was stated above, the basic assumption of this work was that if an animal has been trained with one hemisphere depressed, it cannot then perform when the state of the two hemispheres is reversed; this shows that the memory of the habit must have been confined to the hemisphere which was nondepressed during original learning. Though this is an appealing argument, it is by no means a compelling one, and Schneider has set about showing why it is often wrong. Schneider's alternative hypothesis is that the rat's inability to transfer is due to generalization decrement. It is probable that there is a change in the stimulus complex concomitant with changes of cortical depression. It is also known that changes in stimulus conditions between training and test conditions can lead to apparent forgetting on the part of the animal.

To support his thesis, Schneider has to show that certain propositions are true. The first is that spreading depression can act as a stimulus to the rat. Schneider & Kay (58) trained rats in an operant situation, reinforcing responses emitted under unilateral spreading depression but not reinforcing those with cortex normal. It was found that during extinction more responses were emitted under unilateral spreading depression than without depression. The second proposition which then has to be demonstrated is that stimulus change due to spreading depression does act to interfere with performance. To test this, Schneider (54) trained rats to perform an avoidance task. Some rats were trained under unilateral spreading depression while others were trained with the entire cortex undepressed. Later transfer of both groups to a condition where the cortex was bilaterally depressed showed much larger savings in the case of the animals trained originally under unilateral spreading depression. Schneider (54) interprets this to show that transfer to a state of bilateral spreading depression involves much less of a stimulus change for the animals trained under unilateral spreading depression than for the animals which had not had experience of spreading depression at all.

However, this experiment may be criticized on two grounds. First, no controls were run for the effects of repeated spreading depression. There may be physiological effects due simply to repeated treatment. Second, Schneider (53) purports to show that unilateral spreading depression produces subcortical memory storage. Such subcortical storage, according to him, does not occur when the cortex is undepressed. It seems that this, rather than degrees of stimulus change, could explain his experiment, as he himself states (53).

To counter this objection, Schneider (53) ran another experiment in which he trained rats in a passive avoidance task of the step-down variety. Two groups were trained under unilateral spreading depression. One was subsequently tested under the same unilateral depression, whereas the other was tested with cortex normal. During this test the performance of the rats tested with cortex normal was greatly inferior to those tested under unilateral depression.

Schneider's conclusion has been criticized by Squire & Liss (60) on the

grounds that unilateral spreading depression normally increases latencies and that the longer latencies, and so "better" performance, of the unilaterally depressed rats are a result of motor depression. However, Schneider correctly points out that the two other groups in his experiment which were tested under unilateral spreading depression had even shorter latencies than the normal group whose superior performance Squire & Liss (60) seek to explain on grounds of motor noninvolvement. However, the role of repeated treatment with spreading depression was not evaluated.

It is when we come to his experimental critique of memory transfer from one hemisphere to the other that Schneider's case becomes watertight. The experiment we may consider as a paradigm was carried out by Russell & Ochs (52). They trained rats to lever-press to obtain food while one hemisphere was depressed. This habit did not transfer to the originally depressed hemisphere even after a two-week interdepression period. However, if the animals were given a single rewarded lever-press with both hemispheres nondepressed, the response apparently "transferred" to the originally depressed hemisphere. A number of experiments based on this paradigm have been performed and remarkable inferences about memory trace movements have been drawn.

Schneider & Hamburg (57) trained rats in a shuttle box under unilateral spreading depression. No savings were observed when the rats were retested with the opposite hemisphere depressed. Savings were observed when a trial with unavoidable shock was given between the two sessions with unilateral spreading depression. This is in accord with the previous hypothesis that one trial is needed with both hemispheres undepressed to induce the memory trace to transfer from one hemisphere to the other. However, another group given the unavoidable shock prior to all training and not in the interval between the depression of one hemisphere and then the other showed transfer between the two separately trained hemispheres on a subsequent test. That is, it does not seem to matter whether training in the situation with two hemispheres undepressed takes place before any memory trace has been laid down or after it has been unilaterally laid down. Transfer of training from the condition of one hemisphere depressed to the other depressed takes place in both conditions. This indicates that such transfer cannot be due to the memory trace moving from one hemisphere to the other because of a single reinforced trial conducted in the interval between the depression of one hemisphere and that of the other.

An even more damaging experiment to the interpretation of interhemispheric memory transfer was carried out by Schneider & Ebbesen (56). Their experiment was very similar to that of Russell & Ochs except that they added a control group. Besides the group which was given a rewarded trial with both hemispheres undepressed, another group was given the rewarded trial under identical circumstances except that the rewarded trial was given with the trained hemisphere depressed. Both groups were then tested for responding during extinction with the trained hemisphere depressed. Transfer from the trained to the untrained hemisphere was observed

for both groups. However, the group given the single intervening trial with the trained hemisphere depressed showed very much more transfer than the group given the intervening rewarded trial with both hemispheres undepressed. Here it is difficult to see how a memory trace could have been induced to transfer from a depressed hemisphere to the undepressed hemisphere by the rewarded trial. On the other hand, the result is much more comprehensible in terms of the stimulus generalization hypothesis of Schneider (53).

It seems then that Schneider has cast serious doubt on the conventional explanations of experiments using spreading depression to study memory. Squire & Liss claim (60), however, that he cannot readily explain the results of Albert (4). Albert used the same paradigm as Russell & Ochs (52). That is, he trained a single undepressed hemisphere, then gave an intervening rewarded trial with both hemispheres undepressed, and finally used unilateral spreading depression to produce retrograde amnesia in a single hemisphere. In one set of experiments such depression was applied to the previously trained hemisphere (the transmitting hemisphere); in another set to the previously untrained hemisphere. Albert claimed to measure the consolidation time of the transferred trace. However, though spreading depression causes retrograde amnesia, Bureš (8) has recently shown that such amnesia is only temporary and therefore cannot be considered to prevent consolidation. Schneider (55) attempts an intricate analysis of Albert's experiment to refute Squire & Liss' criticism. The matter can be dealt with more simply. If the original Russell & Ochs' (52) interpretation is erroneous, as Schneider has certainly shown, then Albert's interpretation of his own work which uses Russell & Ochs' basic paradigm and theory must also be fallacious. Further, Schneider does not need to interpret all the data on spreading depression in terms of a single detailed theory based on the notions of generalization decrement and stimulus generalization. Spreading depression has never been a tool of choice for studying such phenomena and one may confidently say it never will be. There are too many unknown confounding factors. The important contribution of Schneider is his demonstration that spreading depression is not a tool of choice for studying memory trace dynamics. The burden of proof is not on Schneider to show that he can explain all the data on his hypothesis, as seems to be assumed by Squire & Liss (60) and Carlson (12). Rather, those wishing to use the method to draw inferences about memory must prove that their results are not due to the serious confounding factors demonstrated by Schneider.

Memory localization—cortical or subcortical.—Inferences from the method of spreading depression have been drawn about whether a particular habit is stored cortically or subcortically (10). If a habit transfers between the condition where one hemisphere is depressed to the condition where the other is depressed, it is concluded that storage must have been subcortical. If the habit does not transfer, the conclusion is drawn that the habit is cortically stored.

Continuing this tradition, Carlson (12) in a series of experiments trained

rats in a box, one half of which was white and the other black. In her first experiment, rats were shocked in one compartment under unilateral spreading depression. In the subsequent test, Carlson measured the time spent in the nonshocked compartment as a index of the memory of emotional and cue aspects, and the latency of entry into the shocked compartment as a measure of the response of passive avoidance. It was found that even when the spreading depression was switched from one hemisphere to the other between training and test, rats would spend more time in the side in which they had not been shocked, indicating memory of emotional and cue aspects. Though there was a large difference in the means of the latencies of entry into the shocked side between experimentals and controls (6.50 to 33.12), this difference in passive avoidance did not reach statistical significance. This is not surprising, as there were only four rats in the control group and eight in the experimental group. What is more surprising is the author's conclusion: "From this it would appear that subcortical structures can store information about emotional and cue aspects of the situation but that 'trained' hemicortex must be functional . . . . for *S* to perform even as simple a response as passive avoidance" (12, p. 425).

In a second experiment, Carlson trained three groups ($N=5$) of rats in avoidance, shocking them in the black compartment until they escaped to the white. One group (S) was trained and tested with unilateral spreading depression always on the same side. A second group (E) was trained with spreading depression on one side and tested under contralateral spreading depression. A third group (C) was given spreading depression on one side but not trained, and then tested under contralateral spreading depression. Group S showed retention both by the time spent in the black side and also by the latency of entry into that side. To assess the test behavior of group E, E could be compared either with its own performance before treatment or with group C. Carlson is not consistent about which comparison is made. Group C was compared with group E to show that side preference had changed for group E as a result of the training of the opposite hemicortex. The change in group E's score before and after treatment was smaller than the difference between E and C. Here a comparison between E and C was made, and it was concluded that emotional and cue aspects were retained and therefore stored subcortically. However, when changes in latency of entry into the black side were assessed, group E was compared against itself. Here the change in latency in group E before and after treatment was small, but the difference between group E and group C was more than threefold. This large difference might support the notion that complex motor responses could also be stored subcortically and contradict Carlson's thesis.

> Thus although *Ss* in group E clearly retained information about the emotional and cue aspects, sufficient to enable them to spend less time overall in the black side, they did not delay their first entry into that side. . . Thus these results support . . . (the) hypothesis that subcortical structures are important in the storage of emo-

tional and cue components, and that the complex motor response must be cortically integrated [Carlson (12), p. 425–26].

Not only are questionable logical methods used to bolster a preconceived hypothesis, but it is also clear that the interpretation of experiments like this can be made in terms of generalization decrement. It may be simply that different degrees of generalization decrement operate for different components of a task and for different tasks and under different motivational conditions.

Schneider (53) has employed another approach to this problem of localizing the memory trace. He has used the fact that spreading depression applied soon after learning produces retrograde amnesia. He reasoned that he could produce retrograde amnesia only in one cortical hemisphere if he applied spreading depression to that hemisphere alone. From results obtained by employing a combination of spreading depression during and just after learning, he concludes that there is subcortical storage if there is spreading depression during training. Otherwise, according to him, the trace resides only in the cortex. However, there are insufficient controls on the role of unilateral or repeated spreading depression on susceptibility to such treatment to permit a conclusive evaluation of Schneider's study. There seems to be no good evidence at present that memory storage in the rat is ever cortical.

Electroconvulsive Shock and Amnesia

The hope behind the many investigations employing ECS seemed to be that "consolidation" of the memory trace could be studied. The notion was that the memory trace shortly after being laid down was labile and susceptible to destruction, but that it soon changed state and became impervious to disruption. If the time that it took the memory trace to consolidate could be measured, some clue to its physical identity might be found. However, no constant time over which ECS disrupts memory after training has been found. For instance, Quartermain, Paolino & Miller (48) and Chorover & Schiller (14) have found an interval in the order of seconds. On the other hand, Kopp, Bohdanecky & Jarvik (39) have found effects 6 hr after training, and McGaugh (42) reports effects on memory 3 hr after training. Some of these discrepancies are due to amount of current passed through the animal. McGaugh (42) demonstrates that length of electroshock is a factor. Jarvik & Kopp (35) show that increased current intensity produces increasing amnesia.

Whether ECS effects are seen at all may be influenced by competing responses. Gerbrandt et al. (33) report failure to find an effect of ECS on memory of a discrimination training using hooded rats. In a subsequent experiment, Bureš and co-workers (11) found such an effect only in albino rats. They did find an adverse effect of ECS on the memory of a reversal habit when overtraining was given on the original habit. This effect was observed both in hooded and albino rats.

The picture of two qualitatively different processes—one susceptible to ECS and the other an invulnerable consolidated memory trace—seems no longer so plausible. That some change is occurring during the footshock-ECS interval has been made clear. However ECS seems to be capable of interfering with memory up to an ill-defined point on a merely quantitatively changing continuum. The notion of a quantitatively changing continuum is supported by the amnesic effects of other agents. For instance, flurothyl (hexafluorodiethyl ether), when compared in efficacy to ECS by Bohdanecky, Kopp & Jarvik (7), showed an effect longer after training than did ECS. The curves of amnesic effect of these two agents presented by Bohdanecky, Kopp & Jarvik (7) run parallel and except for the degree of amnesic effect seem qualitatively similar.

Turning back again to the original hypothesis which appeared to motivate research with ECS, it was hoped to show that there was a phase during which memory was labile and so subject to destruction by ECS. If this were the case, the application of ECS at some interval after learning should lead to a permanent amnesia for the habit learned [Duncan (28)]. Chevalier (13) found no diminution of ECS amnesia after a month. Zinkin & Miller (62) found an apparent recovery of memory after ECS under conditions of repeated testing of a single group. Luttges & McGaugh (41) found no such effect if separate groups were tested at different time intervals, so that each mouse was retested only once. No apparent recovery of memory occurred after one month, even though control animals had not forgotten the task. Kohlenberg & Trabasso (38) on the other hand, found that mice given ECS performed at the same level as controls 48 hr after treatment, but were markedly inferior after only 24 hr. It is to be noted here that there was a considerable degree of forgetting in the controls after 48 hr. Such a trend can also be seen in the data of McGaugh and Alpern [quoted by McGaugh (42)]. Almost complete forgetting in a one-trial escape task after one week has been observed by Deutsch & Yeomans (27). There are, therefore, discrepancies both in the time course of memory after ECS and without ECS.

Some of the differences with respect to recovery of memory after ECS are resolved by Peeke & Herz (46), who showed an apparent recovery in mice 72 hr after learning when such mice had been tested 24 and 48 hr after learning, but no such recovery when mice were tested only 72 hr later. Schneider & Sherman (59) present data which suggest that recovery of memory after ECS occurs when there is stronger initial learning, as produced by increasing the number of footshocks, but not when such learning is weaker. Another possible reason for this discrepancy in the ECS data has been given by Pagano et al. (45). They have shown that whether memory returns after ECS treatment depends upon the intensity of ECS. Relatively low ECS intensity permitted a return of memory of a step-down task within 24 to 48 hr. There was amnesia at one hour after ECS, in contrast with the results of Geller & Jarvik (32). Such amnesia was only observed when ECS was administered 0.5 sec after footshock. No amnesia was observed when the footshock-ECS interval was 30 sec. On the other hand, high ECS in-

tensity led to an amnesia which lasted for 48 hr, the longest time after ECS that the rats were tested.

An interesting sidelight on the initial hypothesis of consolidation which motivated work with ECS is cast by a study of Geller & Jarvik (32). These workers found that memory remains for a few hours after ECS but disappears by 24 hr, the interval after which animals treated with ECS have been traditionally tested. This creates somewhat of a paradox for the simple consolidation model. It is difficult to see how memory could persist after the labile stage of memory has been destroyed by ECS. There are alternate possibilities to explain Geller and Jarvik's result. The first would be to suppose that there were two processes involved, both beginning with the learning experience. The first would be transient and immune to ECS. The second process would normally be long-lasting but ECS could prevent its initiation. This type of explanation has been suggested in connection with the protein synthesis data. A second possible explanation would be to assume that there was a single process and that ECS accelerates forgetting. The data do not compel us to accept a two-stage model.

Perhaps the most damaging criticism of ECS as a tool is that it does not produce a retrograde memory deficit at all. Routtenberg & Kay (51) and Kopp et al. (39) have provided evidence that ECS causes decreased latencies and thus could produce an appearance of amnesia in tests where an increase in latency is taken as evidence of retention. However, such findings by themselves could not explain why somewhat small differences in time of ECS after learning (the retrograde effect) should produce differences in amount of amnesia. However, Schneider & Sherman (59) have now shown why this explanation in terms of reduced latency could fit the retrograde effect. Schneider & Sherman found that the critical variable to produce an appearance of amnesia was the interval between footshock and ECS. When rats were shocked upon stepping off a platform, ECS 0.5 sec later produced amnesia 24 hr later. ECS administered 30 sec or 6 hr later produced no amnesia. However, if a second footshock was given 0.5 sec before the ECS (given either 30 sec or 6 hr later), "amnesia" was produced.

Schneider (personal communication) states that the combination of footshock and ECS can be given outside the test situation, either before or after the step-off task, and apparent amnesia for the step-off task will still result. It seems that some interaction between footshock and ECS is responsible for the quasi-retrograde amnesia normally observed. It is difficult to see how this explanation could be extended to situations where there is an apparent amnesic effect of ECS even where shock is not used before ECS, such as in the study of Peeke & Herz (46). However, the "amnesia" in their experiment may have been a simple performance decrement due to ECS, as no retrograde action of the ECS was demonstrated. There does seem to be an interaction between ECS and footshock. Coons & Miller (16) showed that ECS side-effects were greater if ECS was administered sooner after footshock.

Another experiment casting doubt on the retrograde amnesic nature of

ECS was performed by Misanin, Miller & Lewis (44), who propose a hypothesis which would cover ECS results found in appetitive situations. They trained rats to lick when thirsty. The rats were then exposed to a burst of intense white noise. The offset of this noise coincided with footshock. A control group showed that 24 hr later such noise depressed the rate of licking. The rate of licking was equally unaffected in the group given ECS immediately after the noise-footshock training and in the group where ECS was administered 24 hr later, immediately after a second exposure to the noise. When the white noise was omitted just prior to ECS treatment 24 hr later, memory was not significantly affected, as judged by depression in the rate of licking. The authors explain the result by assuming that ECS has an effect on memory when the memory trace is activated and "that the memory system must be in a state of change at the time of ECS."

The studies just reviewed show how the use of ECS as a technique for the study of consolidation of memory has recently been called into serious question by the experimental evidence. It is not even clear at present in what way, if any, memory is affected by ECS. Earlier we saw how the use of inhibitors of protein synthesis and the use of spreading depression have also run into major problems. However, in spite of, or rather perhaps because of, recent discoveries which are forcing a re-evaluation of old ideas, the study of the physiological bases of memory is entering a new and exciting phase.

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