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Brain Damage, Stress, and Life Span: An Experimental Study[1]

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Mice received frontal pole transections or sham operations, and approximately half in each group experienced cold stress five times throughout their lives. On two occasions certain selected animals were subjected to cold + restraint stress. Neither the brain lesions nor the cold stress affected life span. The stressors, however, were effective in temporarily elevating serum corticosterone levels and, in the case of cold + restraint, producing gastric stress erosions. A significant partial correlation between stress and cause of death was found. This effect appeared to be due primarily to reticulum cell sarcomas metastasizing to the lung (pulmonary tumors) with much greater frequency among animals exposed to stress.

Key Words: Longevity, Brain lesions, Ulcers, Frontal cortex, Corticosterone, Mice

ALTHOUGH it is common knowledge that longevity may be shortened for individuals who have suffered strokes and related brain diseases, virtually nothing is known about longevity in seemingly healthy persons who experience brain injuries from external sources (e.g., missile wounds, industrial accidents), especially those who recover the ability to lead relatively normal lives. Controlled experimentation on how brain damage may affect longevity and disease incidence in this population is needed for several reasons. First, if life span is shortened by brain damage, interventions might be attempted to normalize it. Second, such data would bear directly on decisions to perform psychosurgery or even brain biopsies, both of which, perhaps by damaging the blood-brain barrier and triggering autoimmune reactions (Threatt et al., 1971), conceivably could affect life span. Third, these data would be important to researchers planning and designing experiments to assess the long-term effects of brain injury on physiology and behavior. And fourth, longevity data on brain-injured populations may also provide experimenters with some insight into the concept and nature of an aging pacemaker in the brain. Several investigators (e.g., Denkla, 1977; Dilman, 1976; Finch, 1976; Timiras, 1978) have proposed that the neuroendocrine axis may contain an aging pacemaker. Although most localize such a regulator of the aging process either in the hypothalamus or in the hypothalamic-pituitary segment of the neuroendocrine system, Timiras (1978) has argued that "higher" brain centers may serve as pacemakers through neural connections with the hypothalamus. Some individuals (Denkla, 1977; Dilman, 1976; Finch, 1976), in fact, have proposed that aging-linked diseases may derive from defects in the neuroendocrine system.

Stress also has been regarded as having an influence on longevity and the aging process. Although there is general agreement that with advancing age there is a progressive decline in the capacity to reestablish conditions of equilibrium after a major stressful event, intermittent exposure to such stressors as starvation, cold, electric shock, and water deprivation in adult life may, under some circumstances, actually extend longevity (see Sacher, 1977, for review). In one particularly relevant study on mice, some investigators (Ordy et al., 1967) combined stress (cold and/or electric shock) with deuteron irradiation restricted to the brain. They found that irradiation, which could be thought of as producing a diffuse type of brain damage, significantly decreased longevity in the absence of stress. In contrast, there was a tendency for intermittent stress to increase longevity in both irradiated and control animals, although these effects fell short of being statistically significant.

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The present study was designed to assess further the effects of brain damage on longevity. This study, in which the laboratory mouse was used as a model, is comparable to that of Ordy et al. (1967) in that some animals from the brain lesion group and some from the control group were subjected to intermittent stress. Unlike the earlier experiment, however, this investigation deals with an acute focal lesion (frontal pole transection), rather than the more generalized pathological state caused by deuteron irradiation. Moreover, an attempt was made to identify the various causes of illness and death in each of the different groups; something not attempted in the past.

Methods

Subjects. — More than 300 male C57 BL/6J mice (obtained at about 35 days of age from Jackson Laboratories) were subjected to bilateral frontal pole transections or sham operations when sexually mature (64 to 82 days old). Of these, 144 brain damaged and an equal number of sham-operated mice survived these procedures and were included in the study. All animals were housed in clear plastic cages (29 × 19 × 13 cm) under standard laboratory conditions. Each cage contained approximately eight animals at the start of the study, but this number diminished as animals died or were removed over the course of the investigation. The mice experienced a light/dark cycle of 9 hours on/15 hours off and had unlimited access to food (Purina Rat Chow) and water, except during the stress sessions.

Surgery. — Surgery was conducted following the general procedure used by Glick et al. (1971) for making frontal pole transections in mice. Briefly, animals were anesthetized with methoxyflurane anesthesia (Penthrane, Abbott), and after exposure of the skull, a no. 11 scalpel blade was inserted through the bone 1.5 mm posterior to the tips of the frontal poles. The blade, which penetrated about 1.5 mm of cortex, was swept transversely on each side of the brain to produce cuts in the coronal plane (frontal pole transections). The procedure for the sham operations was identical with that described for the animals with lesions except that a scalpel blade was not inserted. Both groups of animals were sutured with silk thread, and no additional drugs were administered upon completion of surgery or during the recovery period.

Stress procedures. — Approximately half of the mice in the lesion and sham-operated groups were assigned at random to the stress condition. These animals were intermittently exposed to cold stress. Thus, the study involved four groups of animals: frontal lesion + stress (L-St), frontal lesion + no stress (L-NSt), sham operation + stress (S-St), and sham operation + no stress (S-NSt).

The cold stress procedure involved removing food and water from the cages and placing the mice into a ventilated refrigerator that was kept at 10°C (± 1°) for 3 hours. (Nonstressed animals remained in their home cages during these sessions.) The animals experienced the cold stress when 2.5, 9, 16, 20, and 25 months of age. Most animals subjected to these conditions were allowed to live out their lives and die from "natural causes." However, after two of the cold stress sessions (9 and 25 months of age), five animals were killed from each of the four groups to assess the effects of this experience on gastric erosions and serum corticosterone levels, two frequently used indicators of stress.

In addition to sacrificing these animals, mice were killed on three other occasions. At 16 and 20 months of age, five animals from each stress group received a more severe stressor that involved cold + restraint, whereas the other animals in the L-St and S-St groups received only cold stress. In both cases, the 10 stressed animals were killed after the cold + restraint procedure, along with five animals from each of the nonstressed groups, to determine whether the sham-operated and brain-damaged animals would respond differently to the more intense stressor.

The cold + restraint procedure involved sedating the animals with Penthrane, securing them onto a small glass plate by placing tape across the abdomen and appendages, and placing them in the same 10°C refrigerator used for cold stress, but for only 2 hours.

The last sacrifice point occurred when the animals were 30 months of age. At that time five mice were killed from each group under normal home cage conditions (i.e., 5 months after the L-St and S-St animals last experienced cold stress). These data were collected to determine whether the effects of the earlier stress sessions would still be noticeable after a lengthy recovery period.

In summary, animals in the S-St and L-St groups that were allowed to live out their lives experienced five cold stress sessions. Some animals, however, were sacrificed after two of the

cold stress sessions (9 and 25 months), some after experiencing a more severe stressor (cold + restraint at 16 and 20 months), and some that were sampled under nonstressed "resting" conditions later in life (30 months). Gastric erosions and serum corticosterone levels were examined in sacrificed animals, and these mice were also used to assess the general condition of the colony and to determine what diseases the animals were contracting at various points in their lives.

Pathological examinations. — The mice that were sacrificed were transported directly from the refrigerator or their home cages to a room where they were killed by decapitation. Transporting animals and collecting their trunk blood for the corticosterone assay took no more than 2 min. The blood was placed in a centrifuge, and serum samples were separated and frozen at −20°C prior to radioimmunoassay, using the basic method of Foster and Dunn (1974; see Poland et al., 1981). Antiserum was obtained commercially (Radioassay Systems Laboratories, Carson, CA), and the maximum intra- and interassay coefficients of variation, calculated from multiple serum pool replicates, was 12 and 17%, respectively.

After the collection of trunk blood, the mice were laparotomized and, with the esophagus and duodenum clamped, the stomachs were inflated by injection of tap water through the cardia. Each stomach then was removed and placed in a beaker containing 10% formalin solution for 1 min. The stomach then was opened by incising it along the greater curvature and spread out in formalin for further fixing. The next day the stomachs were viewed through a dissecting microscope, and erosions were scored by a judge who was not informed of the group affiliation of each animal. To be considered as a gastric erosion a lesion had to be confined to the glandular portion of the stomach and hemorrhaged necrotic tissue had to be present in the base of the eroded area. This tissue appeared deep red or black in color and could not be easily removed with a cotton-tipped applicator. The frequency of gastric erosions was tabulated, and the presence of any destruction to the rumen (nonglandular portion of the mouse stomach) was noted for each stomach.

All animals in the study (those sacrificed and those allowed to die from natural causes) were subjected to pathological examinations. These examinations involved all major organ systems and were aimed at determining either the cause of death or the presence of diseases that could affect life span in sacrificed animals.

Results

Frontal transections. — Brains with lesions were sampled from sacrificed mice, sectioned on a freezing microtome at 40 μm, and stained with cresyl-violet to reveal more clearly the characteristics of the frontal pole transections. Figure 1 shows a sagittal section of a brain containing a lesion representative of those made in the brain-damaged groups. At their deepest extent, the frontal lesions touched the most anterior part of the corpus callosum. The cuts did not cross the midline but did extend to the lateral surface of the cortex on each side of the brain. These mice showed no obvious behavioral signs of having frontal pole transections.

Indicators of stress. — The means and standard deviations for the corticosterone levels at each sacrifice point appear in Table 1. The results of a series of two by two analyses of variance (unweighted means when appropriate) showed that both cold stress and cold + restraint stress significantly elevated corticosterone levels of both brain-damaged and sham-operated animals sacrificed immediately after the stress procedures (data points 1 to 4; all $ps < .01$). In contrast to this main effect of the stressor, the main effect of the lesion and the lesion-stress interaction did not achieve statistical significance ($ps > .05$). In addition, when corticoster-

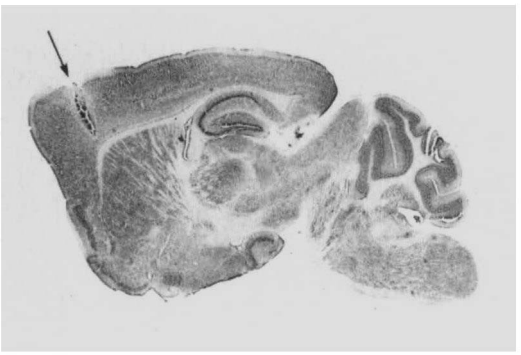

Figure 1. Sagittal section of the brain of a mouse with a frontal pole transection (arrow). This lesion is representative of the frontal transections that extended from the midline to the lateral edges of the cortex just anterior to bregma. The damage, made with a pointed scalpel blade, was confined to the region above the corpus callosum and appeared to be very consistent from animal to animal (see text).

one levels were assessed in animals under basal resting conditions 5 months after the last stress session, no main or interaction effects were significant.

Means and standard deviations of the frequency of gastric erosions following cold + restraint (data points 2 and 3) are presented in Table 2. Although no significant main or interaction effects were found in the first of these sessions, the stress variable approached statistical significance ($p < .10$). A two by two analysis of variance revealed a significant main effect of stress in the second cold + restraint session ($p < .05$). The milder cold stress (without restraint) had negligible effects on stomach pathology in all instances.

Longevity. — Figure 2 graphically presents the longevity data collected for the four groups of mice. As can be seen, all groups showed comparable mean longevity scores (low of 27.94 to high of 29.80), standard deviations, and profiles. Very few animals died when less than 20 months of age, and very few lived beyond 36 months of age. The results of a two by two analysis of variance (unweighted means) conducted on the life spans (months lived) of the mice that died from natural causes revealed no significant main or interaction effects due to brain damage or stress.

Table 1. Means and Standard Deviations: Serum Corticosterone Levels (μg/dl)

Data points			Groups			
Age (months)	Stressor type		S-St	L-St	S-NSt	L-NSt
9	cold	*M*	10.04	12.53	.88	2.08
		SD	5.09	5.16	.61	1.73
		N	5	4	5	5
16	cold + restraint	*M*	27.98	25.85	2.68	7.20
		SD	7.03	4.82	1.59	4.93
		N	4	4	5	4
20	cold + restraint	*M*	30.42	27.54	2.66	1.06
		SD	6.95	9.45	3.70	.32
		N	5	5	5	5
25	cold	*M*	13.66	10.86	1.28	3.54
		SD	7.17	5.09	.67	3.15
		N	5	5	5	5
30	basal resting	*M*	3.34	5.94	1.52	2.68
		SD	2.84	8.04	.57	1.92
		N	5	5	5	5

Table 2. Means and Standard Deviations: Gastric Erosion Scores

Data points			Groups			
Age (months)	Stressor type		S-St	L-St	S-NSt	L-NSt
16	cold + restraint	*M*	6.60	1.20	.60	.60
		SD	6.58	2.68	1.34	1.34
		N	5	5	5	5
20	cold + restraint	*M*	6.00	10.00	1.80	1.80
		SD	5.15	10.20	1.79	1.48
		N	5	5	5	5

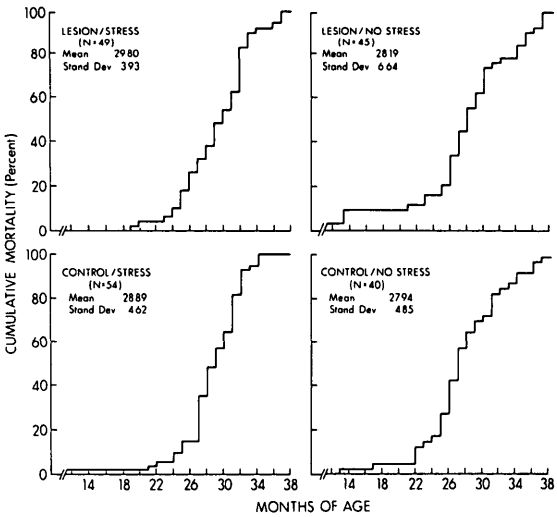

Figure 2. Cumulative mortality rates as a function of surgical and stress treatments.

Lesions associated with death. — The principal diseases associated with death in these mice were pulmonary adenomatosis, metastatic pulmonary tumors, reticulum cell sarcoma, leukemia, and pneumonia. The microscopic character of some of these lesions are shown in Figure 3. Pneumonia was most often of the bronchial type but sometimes involved a total lobe of the lung. When pneumonia was present in the absence of other diseases, it was considered to be the cause of the death. However, it also was frequently present in association with other diseases, particularly pulmonary adenomatosis. When this occurred the pneumonia was considered to be secondary, and the other disease was recorded as the cause of death. Although adenomas of the

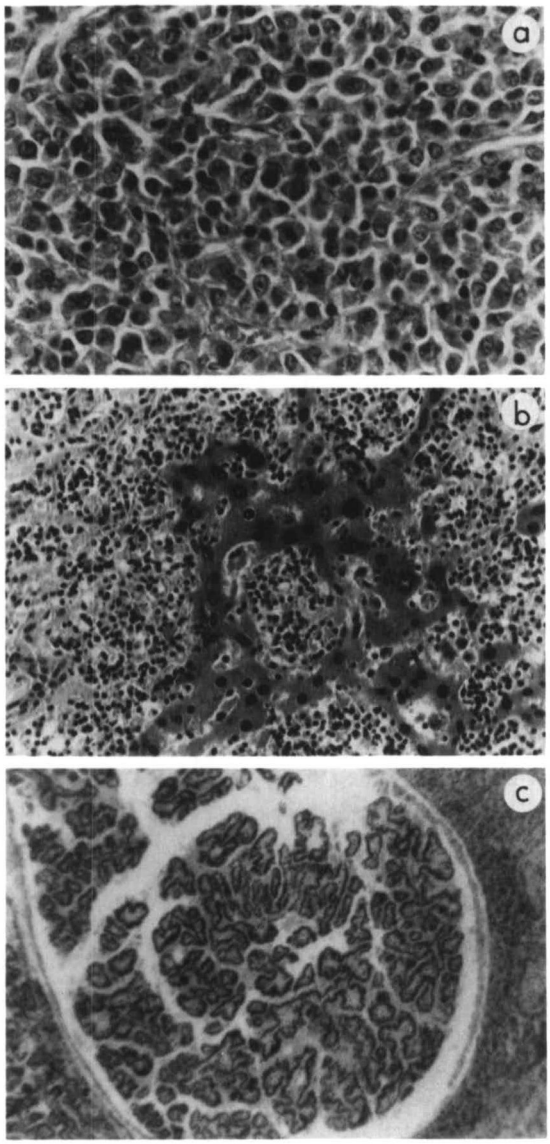

Figure 3. Photomicrographs showing three types of pathology occasionally seen at the time of death. a, Reticulum cell sarcoma of spleen; b, leukemia cell infiltration of liver; and c, adenoma obstructing bronchus of lung surrounded by a consolidating pneumonia.

lung were histologically benign, these tumors were frequently large and multiple at the time of death, producing obstructions of the pulmonary tree. The primary site of the reticulum cell sarcomas appeared to be the spleen which was markedly enlarged; frequently, there was extension (metastasis) to the liver, also usually massive. The leukemias generally exhibited marked infiltration of both liver and spleen. Some mice with reticulum cell sarcoma also showed metastasis to the lungs (all were in stressed animals; five S-St; three L-St). In these cases the cause of death was judged to be metastatic pulmonary tumors. There also were mice with amyloid of the renal glomeruli or the lungs. Some also showed granulomatous myocarditis.

The frequencies of the most common diseases as a function of surgery and stress condition are shown in Table 3. These frequencies represent diseases that were judged to be the cause of death in the animals that were allowed to die from natural causes. The classification, "other," represents animals that succumbed to diseases other than the five most prevalent causes of death or cases in which no cause of death could be found. Animals whose causes of death could not be determined due to autolysis or mutilation were excluded from statistical analysis.

The degree to which lesion, stress, and cause of death were related was assessed through the use of the BMDP 3F computer program for multiway frequency table analysis which employed a log-linear model (tables available on request; see Fienberg, 1979, for a thorough description and explanation of multiple contingency table analysis of cross-classified data).

On the basis of the multiple contingency table analysis where A = stress, B = lesion, and C = cause of death, it was determined that the best fitting, most parsimonious model was (AB)(AC), thus implying a significant partial correlation between stress and cause of death (the AB effect is not of interest since the two variables are fixed). The acceptability of this model was determined by reference to the following findings. First, it was found that the (A)(B)(C) model did not provide a good fit for the data, $G^2(16) = 26.17$, $p \leq .05$, and that the model (AB)(BC)(AC) did provide a good fit, $G^2(4) = 5.07$, $p > .05$. Beginning with the model (AB)(BC)(AC), the deletion of (AC) resulted in

Table 3. Frequencies of Diseases Associated with Natural Deaths

Disease	Group			
	S-St	L-St	S-NSt	L-NSt
Leukemia	17	12	16	10
Pneumonia	14	13	8	10
Reticulum cell sarcoma	4	0	5	5
Metastatic pulmonary tumor	5	3	0	0
Pulmonary adenoma	2	4	0	4
Other	7	13	7	6
Total	49	45	36	34

a significant decrease in the goodness of fit, $G^2_{diff_{AC}}(6) = 13.23$, $p < .05$, whereas the fit was not affected significantly by the deletion of (BC), $G^2_{diff_{BC}}(5) = 7.91$, $p > .05$.

The estimates of the log-linear parameters divided by their standard errors for the (AC) effect showed that two diseases were major contributors to this effect, namely reticulum cell sarcoma, $\lambda/\sigma_{(\lambda)} = 2.15$, $p < .032$, and metastatic pulmonary tumor, $\lambda/\sigma_{(\lambda)} = 3.08$, $p < .002$, where reticulum cell sarcoma as cause of death was negatively related to the cold-stress variable and metastatic pulmonary tumor positively related (statistical tables are available on request). These p values were determined using the asymptotic normality of the ratios without any adjustment for the effect of multiple comparisons. However, it should be noted that the probability that either effect is due to chance is extremely low.

Among the animals that were sacrificed during the course of the experiment, very little evidence of disease was noted prior to the second year of life. At that time the mice seemed to show similar disease profiles to the animals mentioned above that were not sacrificed.

Discussion

In the present study the average life span (27.9 months) of the mice that did not receive frontal cortex transections or stress (i.e., group S-NSt) is consistent with the longevity data reported for C57BL mice by other investigators (e.g., 26.6 months, Rowlatt et al., 1976). Moreover, it can now be concluded that neither stress nor frontal pole transection alters the life spans of these animals. Nevertheless, it was noted that intermittent exposure to cold stress increased the probability of finding metastatic pulmonary tumors. Although the nonstressed groups showed a greater probability of death due to reticulum cell sarcomas, it must be emphasized that the malignant pulmonary tumors noted among the stressed animals originated from these sarcomas. In this sense the negative relationship found between the reticulum cell sarcomas and stress should be viewed as an artifact of the present classification system. The appearance of metastatic pulmonary tumors in the stressed groups is especially interesting because the presence of another tumor of the lung (pulmonary adenomas) did not appear to be affected by the stress variable.

Sklar and Anisman (1979) recently reported that the growth of (experimentally induced) mastocytomas in male mice was augmented by exposing the animals to a stressful situation in which they were unable to execute effective coping responses. They noted that a single stress session involving inescapable shock produced an earlier appearance of the tumor, an enlargement of its size, and abbreviated survival time. The fact that we observed a significant positive correlation between spread of malignancy from the spleen to the lungs under conditions of stress would be consistent with these data. Nevertheless, it should be emphasized that many aspects of this finding remain to be fully determined, including its replicability and ability to generalize across other experimental conditions.

Although intermittent stress has been reported to increase longevity under certain circumstances (Sacher, 1977), the data reported here are not strongly supportive of the generality of this finding, although the main effect of stress did approach statistical significance ($p < .10$). Ordy and colleagues (1967) reported a similar nonsignificant trend. Thus, although some experiments seem to show that stressors such as cold are capable of lengthening life span in some species (see review by Liu & Walford, 1972), the present data, and those of Ordy and his coworkers, suggest that the chronicity of exposure to the stressor, and many other factors, can affect the results of these experiments.

The immediate effects of the cold stress and cold + restraint procedure were straightforward. Both stressors significantly elevated the levels of serum corticosterone at each observation point, and the corticosteroid levels of both stressed and nonstressed animals were consistent with the radioimmunoassay-determined adrenocorticoid response to restraint reported for mice by Redgate and Eleftheriou (1978). The fact that the frontal pole transections had no effect on stress-mediated serum corticosterone concentrations was equally clear. Brain-damaged animals were never found to have circulating corticosteroid levels that were significantly different from the levels observed in sham-operated mice. Furthermore, neither brain lesions nor earlier exposures to stress significantly altered the basal serum corticosterone concentrations of animals tested under home cage "resting" conditions at 30 months of age.

The cold + restraint procedure was found to affect the frequency of gastric erosions, whereas cold stress alone was not effective in this regard. The cold + restraint effect, however, was statistically significant only when the mice were tested

at 20 months of age: Animals exposed to cold + restraint at 16 months tended to have more gastric erosions than nonstressed animals, but this effect was not statistically significant.

The relatively low gastric erosion scores exhibited by some of the animals, especially at 16 months of age, could be due to the fact that the mice were not food deprived before the start of the stress sessions and that some may have just finished eating at that time. During stress food in the stomach protects against the formation of erosions and acute ulcers in both rats (Wozniak & Goldstein, 1980) and mice (Frisone & Essman, 1965). The decision not to deprive the animals before the stress sessions in the present study was based on Frisone and Essman's (1965) finding that food deprivation by itself may produce significant pathological responses in the stomach of the mouse.

Although transecting the frontal cortex did not produce any alterations in adrenocorticoid levels or in gastric pathology in response to mild (cold) or more intense (cold + restraint) stressors, it is known that lesions placed in other parts of the brain can affect these stress responses. In particular, hypothalamic damage and lesions affecting subcortical structures associated with the hypothalamus have been found to significantly alter adrenocorticoid stress responses (e.g., Heyback et al., 1979; Seggie & Brown, 1976; Usher et al., 1967) and stress-induced gastric pathology (e.g., Henke, 1980; Kim et al., 1976). For example, Eli et al. (1977) and Murphy et al. (1979) assayed circulating corticosterone levels in mice and rats that received hippocampal lesions, sham operations, or damage to the cortex overlying the hippocampus. In both studies no differences in plasma corticosterone levels were found between the groups under nonstressful conditions. When stressed, however, the animals with hippocampal lesions showed significant elevations of circulating corticosteroids relative to the control animals, whereas the animals with cortical lesions did not differ from the control group.

It has been known since Cushing's (1932) classic article that damage to various parts of the central nervous system may produce severe, even life-threatening, gastric pathology. Although much experimental attention has been devoted to ulcers of neurogenic origin, little research has focused on the stomach's vulnerability to stress-related pathology after the organism no longer appears severely incapacitated by the brain trauma. In two especially pertinent studies Kim et al. (1976) and Murphy et al. (1979) found that hippocampectomized rats displayed significantly greater pathology after restraint or restraint + shock than normal animals or those with damage to the cortex overlying the hippocampus. In addition, Henke (1980) reported that gastric pathology after restraint was attenuated in rats with bilateral lesions in the amygdaloid complex or in the ansa lenticularis. Lesions in the stria terminalis, in contrast, significantly potentiated the gastric stress response in the latter study.

In summary, the results of many experiments show that damage to the central nervous system can alter the physiological response to stress, but that these effects may depend upon both the site and extent of the damage. Although the most effective lesions seem to involve the hypothalamus or limbic structures directly associated with the hypothalamus (e.g., the hippocampus), many questions still remain to be answered about these effects. The data collected in the present investigation are consistent with earlier reports in suggesting that small, focal lesions of the cerebral cortex may have only a negligible effect in altering an organism's susceptibility to stress (Eli et al., 1977; Kim et al., 1976; Murphy et al., 1979). Whether larger lesions or damage to other structures, especially those far removed from the hypothalamic-anterior pituitary-adrenocortical axis, also will have minimal effects on these indices of stress still remains to be explored.

Finally, with regard to the idea that higher brain centers may contain an aging pacemaker (Timiras, 1978), the present study suggests that, if this concept is valid, it appears unlikely that this role is confined to the frontal cortex or directly a function of this brain area. However, future work involving, for example, large ablations rather than transections, is necessary before more definitive statements can be made about the role of the frontal cortex in the aging process.

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