tered world'' hypothesis as the possible etiological agent. However, the data further validate the rhesus monkey as an animal model for the human visual system, since such a subtle effect is present for both species.

One possible explanation for the lack of agreement between the electrophysiological studies dealing with the distribution of preferred stimulus orientation for neurons in the monkey's striate cortex may stem from the fact that these studies have not analyzed orientation tuning for the various separate categories of cortical neurons. Although attempts to behaviorally demonstrate an oblique effect in cat have failed (*16*), Hirsch and Leventhal have shown that a significant orientation anisotropy exists in the cat's striate cortex for neurons that have small receptive fields and that require slow stimulus movement. These neurons presumably receive afferent input from the sustained or X cell population in the lateral geniculate nucleus and probably process information concerning high spatial frequency. Since the oblique effect is observed only for stimuli of high spatial frequency, the orientation tuning of cortical cells having high spatial-frequency tuning, small receptive fields, and preferring slow stimulus movement should be investigated in the monkey (*17*).

The demonstration of an oblique effect in monkeys provides additional information that the monkey processes spatial information as humans do and bridges the gap between the psychophysical data on humans and neurophysiological data on laboratory animals.

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References and Notes

1. G. C. Higgens and K. Stultz, *J. Opt. Soc. Am.* **38**, 756 (1948); J. C. Ogilvie and M. M. Taylor, *ibid.* **48**, 128 (1958); M. M. Taylor, *ibid.* **53**, 763 (1963).
2. F. W. Campbell, J. J. Kulikowski, J. Levinson, *J. Physiol. (London)* **187**, 427 (1966); D. E. Mitchell, R. D. Freeman, G. Westheimer, *J. Opt Soc. Am.* **57**, 246 (1967).
3. M. A. Berkley, F. Kitterle, D. W. Watkins, *Vision Res.* **15**, 239 (1975); D. E. Mitchell, R. D. Freeman, M. Millodot, G. Haegerstrom, *ibid.* **13**, 535 (1973); R. D. Freeman, D. E. Mitchell, M. Millodot, *Science* **175**, 1384 (1972); D. E. Mitchell and F. Wilkinson, *J. Physiol. (London)* **243**, 739 (1974); R. D. Freeman and L. N. Thibos, *ibid.* **247**, 687 (1975). It has often been hypothesized that orientation anisotropy results from humans' living in a carpentered world and being exposed to a preponderance of horizontal and vertical contours during their early visual development [R. C. Annis and B. Frost, *Science* **182**, 729 (1973)].
4. S. C. Leehey, A. Moskowitz-Cook, S. Brill, R. Held, *Science* **190**, 900 (1975).
5. M. J. Meyer, *Vision Res.* **17**, 703 (1977); D. Y. Teller, R. Morse, R. Borton, D. Regal, *ibid.* **14**, 1433 (1974).
6. J. Gwiazda, S. Brill, I. Mohindra, R. Held, *ibid.* **18**, 1557 (1978).
7. R. J. W. Mansfield, *Science* **186**, 1133 (1974).
8. ——— and S. F. Ronner, *Brain Res.* **149**, 229 (1978).
9. B. L. Finlay, P. H. Schiller, S. F. Volman, *ibid.* **105**, 350 (1976); G. F. Poggio, R. W. Doty, W. H. Talbot, *J. Neurophysiol.* **40**, 1369 (1977).
10. Data from evoked potentials in humans and monkeys and reaction time experiments in humans also show that the oblique effect is present at suprathreshold contrasts [(*8*); L. Maffei and F. W. Campbell, *Science* **167**, 386 (1970); F. Attneave and R. K. Olson, *J. Exp. Psychol.* **74**, 149 (1967)].
11. F. W. Campbell and D. G. Green, *J. Physiol. (London)* **181**, 576 (1965).
12. R. S. Harwerth and H. G. Sperling, *Vision Res.* **15**, 1193 (1975).
13. In order to discourage the monkey from holding through the limited hold time on two consecutive trials to raise the contrast of the grating to a level at which he could perform more easily, a probability factor was introduced with the second hold-through trial. Each hold-through, after the first, had a probability of 0.5 of resetting the grating to full contrast.
14. J. M. Camisa, R. Blake, S. Lema, *Perception* **6**, 165 (1977).
15. R. J. W. Mansfield, *Vision Res.*, **13**, 2219 (1973); J. A. J. Roufs, *ibid.* **14**, 853 (1974); D. B. Moody, in *Animal Psychophysics: the Design and Conduct of Sensory Experiments*, W. C. Stebbins, Ed. (Appleton-Century-Crofts, New York, 1970), pp. 227-301; W. C. Stebbins, *J. Exp. Anal. Behav.* **9**, 135 (1966).
16. S. Bisti and L. Maffei, *J. Physiol. (London)* **241**, 2016 (1974); R. Blake, in *Frontiers in Visual Science*, S. J. Cool and E. L. Smith III, Eds. (Springer-Verlag, New York, 1979); H. V. B. Hirsch and A. G. Leventhal, in *ibid.*
17. Recent behavioral evidence on human infants also suggests that these neurons may mediate the oblique effect (*6*).
18. Supported by NIH grants R01 EY01139, K07 EY00052, and F32 EY015168.

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Stress and Coping Factors Influence Tumor Growth

Abstract. *Growth of syngeneic P815 mastocytoma in DBA/2J male mice was evaluated as a result of various stress regimens. A single session of inescapable shock resulted in earlier tumor appearance, exaggeration of tumor size, and decreased survival time in recipient animals. Escapable shock had no such effects. The effects of the inescapable shock were mitigated if mice received long-term shock treatment.*

Inconsistent and often contradictory results have been reported concerning the effects of stress on tumor growth. Whereas some investigators have reported stress-induced exacerbation of tumorigenicity (*1*, *2*), others have found stress to retard tumor growth (*3*). Interpretation of these results is complicated by the lack of between experiment consistency concerning the species, tumor system, and stressor used, as well as the methods of assessing tumor growth. Nevertheless, there is some suggestion that the severity and chronicity of the stress determine the effects on tumor development (*1*-*3*). Moreover, given the differential effects of controllable and uncontrollable stress on other physiological pathologies (*4*) as well as neurochemical activity (*5*), the possibility should be considered that coping processes may play a role in determining the stress effect on tumor development.

We have examined the effects of coping mechanisms and chronicity of stress on tumor development. A total of 90 DBA/2J male mice (20 to 23 g), housed five per cage and permitted unlimited food and water, were studied in the initial experiment to evaluate tumor development following a single session of inescapable shock. Mice received a subcutaneous injection in the left flank region of 6.25×10^4 viable syngeneic P815 mastocytoma cells suspended in 0.25 ml of RPMI-1640 medium. This dose was selected on the basis of earlier results showing that this number of cells resulted in tumor appearance (defined as 3 mm^2) within 7 to 9 days in all animals (*6*). The P815 cells, which were acquired from a donor mouse bearing an ascites tumor, were washed twice in RPMI-1640 after being extracted and then suspended in this medium for injection. Viability was assessed with trypan blue.

Twenty-four hours after tumor cell transplantation, the animals were individually placed in the shock apparatus for their only shock session. The shock apparatus consisted of six black Plexiglas chambers measuring 30 by 14 by 15 cm. Shock (a-c, 60 Hz) was delivered through a 3000-V source to the grid floor, which was composed of 0.32-cm stainless steel rods 1.0 cm apart and connected through neon bulbs (*7*).

Independent groups of mice received either 1.1, 2.2, or 3.3 hours of apparatus exposure. These groups were divided into subgroups of ten each such that animals in each group were exposed to shock of 75 or 150 μA, or no shock. Shock presentations 6 seconds long were delivered at 1-minute intervals. Tumor size was measured horizontally and vertically with vernier calipers over the 14-day period after cell transplantation. Since tumors grew in somewhat irregular shapes, the largest dimensions perpendicular to one another were chosen in all instances. An approximation of the area of each tumor was obtained by multiplying the two measurements for each animal. The reliability of this measure within and between raters exceeded .80,

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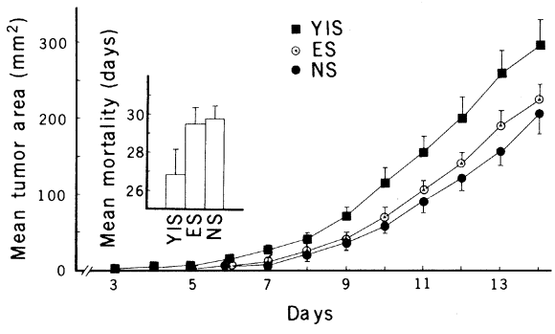

Fig. 1. Mean (± S.E.) tumor area over days, as well as mean day of mortality (inset) among mice that received escapable shock (*ES*), yoked inescapable shock (*YIS*) or no shock (*NS*).

and the correlation between tumor area and tumor weight among 54 additional animals was .85 ($P < .001$).

The day of tumor appearance was significantly influenced by shock stress [$F(2, 81) = 5.47$, $P < .01$]. Consistent with reports indicating stress-induced exacerbation of tumor development (*1, 2*), multiple comparisons (*8*) revealed earlier mean appearance of tumors among the 75- and 150-μA groups ($\bar{X} = 5.7 \pm 0.30$ and 5.8 ± 0.28 days, respectively) relative to nonshocked mice (6.87 ± 0.24 days). In accordance with these results, tumor area also varied as a function of shock over days [$F(26, 1053) = 4.78$, $P < .001$]. Both shock groups displayed significantly larger tumors than control animals on days 9 through 14 (*8, 9*). Predictably, mean day of mortality also varied with shock treatment [$F(2, 81) = 12.61$, $P < .001$], with mice of both shock groups ($\bar{X} = 24.3 \pm 0.723$ and 24.233 ± 0.688 days for 75- and 150-μA groups, respectively) dying significantly earlier than nonshocked controls ($\bar{X} = 29.233 \pm 0.928$ days) (*8*). The 75- and 150-μA groups did not differ from one another on any of the dependent measures, and 1.1 hour of shock exposure yielded effects that did not differ significantly from the 2.2- and 3.3-hour treatments (*10*).

The possibility that the inability to cope behaviorally with stress, rather than the stress per se, was responsible for the exaggerated tumor size was assessed in experiment 2. The shock apparatus consisted of three identical black Plexiglas shuttle boxes measuring 29.2 by 8.9 by 16.5 cm. The two compartments of each shuttle box were separated by a horizontally moving gate. The grid floor and shock source were the same as that of experiment 1 (*7*). The gate separating the two compartments opened 5 seconds after shock onset, thereby assuring that the duration of shock that mice received approximated the 6 seconds used in experiment 1.

Thirty male DBA/2J mice were subcutaneously injected with 6.25×10^4 viable syngeneic P815 cells in the left flank area and exposed to stress 24 hours later. One group of mice received one session of 60 escapable shocks (150 μA) at 1-minute intervals between trials. Mice of a second yoked group were unable to escape shock, and shock offset only occurred when their respective partners of the first group made a successful escape response. Thus, the shock delivered was the same in both these groups, but only the escape group could control shock offset. The third group was placed in the shuttle boxes for an equivalent shock-free period ($N = 10$ per group). The mean escape latency, and therefore the mean shock duration for both the escapable and inescapable shocked animals was 6.29 seconds per trial.

The mean day of tumor appearance varied as a function of shock treatment, [$F(2, 27) = 4.0$, $P < .05$], with tumors among mice that received yoked inescapable shock ($\bar{X} = 5.8 \pm 0.512$ days) appearing significantly earlier than those of the no-shock controls ($\bar{X} = 7.3 \pm 0.578$ days) or the animals that received escapable shock ($\bar{X} = 7.7 \pm 0.396$ days). The latter two groups did not differ significantly from one another in this regard (*8*). Daily group differences in tumor size corresponded to the data on day of appearance (Fig. 1). That is, tumor size varied as a function of the shock treatment over days [$F(26, 351) = 3.66$, $P < .001$], with the yoked inescapably shocked mice exhibiting significantly larger tumors than did the other two groups on days 10 through 14 (*8*). Animals that received escapable shock did not differ from the no-shock mice, with the exception of day 13, when larger tumors were seen among animals that could escape. Although experiment 1 indicated that stress shortens survival time, the difference in survival time between the yoked inescapably shocked mice and escapably shocked or the no-shock mice did not reach an acceptable level of statistical significance ($P = .10$) (Fig. 1). The inconsistency of the size and mortality measures may result from tumor size not being strongly related to survival time, since death occurs as a result of peritoneal invasion and subsequent internal hemorrhage. The absence of a significant mortality effect notwithstanding, the results of experiment 2 strongly indicate that inability to cope with the stress behaviorally, rather than the physical stress per se, was responsible for the effects of shock on tumor size.

The third experiment was designed to determine if acute and chronic exposure to inescapable shock would differentially affect tumor development. Forty male DBA/2J mice were injected subcutaneously with 6.25×10^4 viable syngeneic P815 cells in the left flank region. Beginning 24 hours after cell transplantation, one group of mice received 60 inescapable 6-second shocks (150 μA) at 1-minute intervals between shocks; a second group received five such shock sessions on consecutive days; a third group received ten such shock sessions on consecutive days; and a fourth group was placed in the shock boxes for an equivalent shock-free period on ten consecutive days.

The day of tumor appearance in experiment 3 was somewhat retarded relative

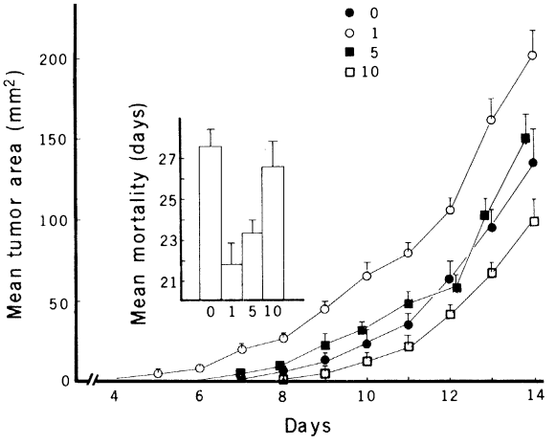

Fig. 2. Mean (± S.E.) tumor area over days, as well as mean day of mortality (inset) among mice that received no shock (●), one session of inescapable shock (○), five sessions of inescapable shock (■), or ten sessions of shock (□).

to that in experiments 1 and 2. Nevertheless, the mean day of tumor appearance again varied as a function of the shock treatment [$F(3, 36) = 20.96$ $P < .001$]. Mice exposed to only one inescapable shock session exhibited tumors significantly earlier ($\bar{X} = 5.9 \pm 0.30$ days) than the mice among the remaining groups (*8*). Likewise, tumors among mice exposed to five sessions of inescapable shock appeared significantly earlier ($\bar{X} = 7.6 \pm 0.34$ days) than did those of mice exposed to ten shock sessions ($\bar{X} = 9.7 \pm 0.396$ days) or no shock ($\bar{X} = 8.7 \pm 0.367$ days). The difference between the latter two groups approached, but did not reach, an acceptable level of significance (*8*). The mean tumor size over days (Fig. 2) followed from these initial differences, in that mean tumor area varied over days as a function of the shock treatment ($F(39, 468) = 8.95$, $P < .001$). Mice that received a single shock session had significantly larger tumors than did the remaining groups on days 9 through 14. The no-shock control animals and mice that experienced five shock sessions did not differ from one another, but they had significantly larger tumors than did the ten-session group on days 12 to 14 (*8*). Finally, day of death (Fig. 2) revealed that shock treatment influenced mortality [$F(3, 36) = 7.02$, $P < .001$]. As noted earlier, a single session of shock decreased survival time relative to no-shock controls. Five shock treatments likewise reduced survival time, but this effect was absent in the ten-session group. It will be noted that, as in experiment 2, the growth and mortality measures, although roughly comparable, were not entirely congruent.

At first blush it seems paradoxical that tumor exacerbation was not apparent after repeated shock. That is, since tumor appearance begins 48 to 72 hours after a single shock session, tumors in the groups that received five or ten shock sessions should have appeared well before the conclusion of the stress regimen. It is possible that certain physiological aftereffects of shock promote tumor development, but that these physiological states are precluded with repeated shock. Alternatively, stress may differentially influence cells that have been recently transplanted and cells that have had the opportunity to adhere and vascularize over a number of days.

Stress may influence tumorigenicity; however, such an effect is dependent on whether control over stress is possible, as well as on the chronicity of the stress regimen. It is premature to ascribe mechanisms for the stress-induced tumor augmentation and inhibition. Neurochemical, hormonal, and immunological mechanisms may all be involved, although the importance of the latter two in mediating the effect of stress has been questioned (*1, 11*). Indirect support for the involvement of central transmitters has come from studies showing modification of tumor development following catecholaminergic manipulations (*12*).

Our data lend credence to the human experimentation that provisionally suggests a role for stress in the development of carcinoma (*13*). This is of particular importance since the human research conducted to date has by and large been of a retrospective nature, has not evaluated the psychological factors associated with stress, and has not considered the importance of stress application relative to different stages of tumor development (*13*). Of course, in order to draw a parallel between animal and human work, it is necessary to determine to what extent different tumor systems are influenced by stress, as well as the role of stress upon tumor induction and metastases.

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References and Notes

1. R. J. Jamasbi and P. Nettesheim, *Br. J. Cancer* **36**, 723 (1977); L. J. Peters, *ibid.* **31**, 293 (1975); ——— and H. Kelly, *Cancer* **39**, 1482 (1977).
2. R. Ader and S. B. Friedman, *J. Comp. Physiol. Psychol.* **59**, 361 (1965); A. Amkraut and G. F. Solomon, *Cancer Res.* **32**, 1428 (1972). See review by R. C. Labarba, *Psychosom. Med.* **32**, 259 (1970).
3. L. L. Gershben, I. Benuck, P. S. Shurrager, *Oncology* **30**, 429 (1974); N. Molomut, F. Lazere, L. W. Smith, *Cancer Res.* **23**, 1097 (1963); B. H. Newberry *et al.*, *Psychosom. Med.* **34**, 295 (1972); B. H. Newberry, J. Gildow, J. Wogan, R. L. Reese, *ibid.* **38**, 1955 (1976); S. N. Pradhan and P. Ray, *J. Natl. Cancer Inst.* **53**, 1241 (1974); H. A. Rashkis, *Science* **116**, 169 (1952).
4. J. M. Weiss, *J. Comp. Physiol. Psychol.* **77**, 1 (1971); *ibid.*, p. 14; *ibid.*, p. 22.
5. H. Anisman, in *Psychopharmacology of Aversively Motivated Behavior*, H. Anisman and G. Bignami, Eds. (Plenum, New York, 1976), pp. 119–172; J. N. Hingtgen, J. E. Smith, P. A. Shea, M. H. Aprison, T. M. Gaff, *Science* **193**, 332 (1976); R. Kvetnansky, A. Mitro, M. Palkovitz, M. Brownstein, T. Torda, M. Vigas, L. Mikulajin, in *Catecholamines and Stress*, E. Usdin, R. Kvetnansky, J. J. Kopin, Eds. (Pergamon, Oxford, 1976), pp. 39–50; E. A. Stone, in *Catecholamines and Behavior*, A. J. Friedhoff, Ed. (Plenum, New York, 1975), vol. 2, p. 31–72; A. M. Thierry, G. Blanc, J. Glowinski, *J. Neurochem.* **18**, 449 (1971); J. M. Weiss, E. A. Stone, M. Harrell, *J. Comp. Physiol. Psychol.* **72**, 160 (1970). J. M. Weiss, H. I. Glazer, L. A. Pohorecky, in *Animal Models in Human Psychobiology*, G. Serban and A. Kling, Eds. (Plenum, New York, 1976), pp. 141–173.
6. L. S. Sklar and H. Anisman, *Soc. Neurosci. Abstr.* **4**, 400 (1978).
7. H. Anisman, D. Decatanzaro, G. Remington, *J. Exp. Psychol. Anim. Behav. Proc.* **4**, 197 (1978).
8. Newman-Keuls multiple comparisons ($\alpha = .05$) were carried out in all instances.
9. Mean [± standard error (S.E.)] on days 9 to 14: no shock = 37.18 ± 4.20, 63.0 ± 5.72, 99.21 ± 8.16, 138.62 ± 9.61, 185.16 ± 10.73, and 219.79 ± 10.63; 75 μA = 64.45 ± 4.82, 91.34 ± 6.97, 132.51 ± 8.54, 168.16 ± 9.78, 231.29 ± 12.06, and 284.69 ± 15.34; 150 μA = 66.66 ± 5.9, 97.62 ± 6.99, 142.80 ± 9.98, 188.40 ± 9.82, 242.03 ± 15.29, and 291.73 ± 20.89.
10. Mean day of appearance (± S.E.) for the 1.1, 2.2, and 3.3 hours of shock exposure: 5.95 ± 0.47, 6.0 ± 0.56, and 5.40 ± 0.52 days, respectively; $P > .10$. Mean survival time (± S.E.) for the 1.1, 2.2, and 3.3 hours of shock exposure: 23.65 ± 1.19, 24.70 ± 1.27, and 24.30 ± 1.32 days, respectively; $P > .10$.
11. A. A. Monjan and M. I. Collector, *Science* **196**, 307 (1977).
12. G. C. Cotzias and L. C. Tang, *ibid.* **197**, 1094 (1977); G. C. Cotzias, S. T. Miller, L. C. Tang, P.S. Papavasiliou, Y. Y. Wang, *ibid.* **196**, 549 (1977); M. M. Wick, *Nature (London)* **269**, 512 (1977); *Science* **199**, 775 (1978).
13. B. H. Fox, *J. Behav. Med.* **1**, 45 (1978).
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Dissociations Between the Effects of LSD on Behavior and Raphe Unit Activity in Freely Moving Cats

Abstract. *The hypothesis that the action of hallucinogenic drugs is mediated by a depression of the activity of brain serotonergic (raphe) neurons was tested by examining the behavioral effects of* d*-lysergic acid diethylamide (LSD) while studying the activity of raphe neurons in freely moving cats. Although the results provide general support for the hypothesis, there were several important dissociations. (i) Low doses of LSD produced only small decreases in raphe unit activity but significant behavioral changes; (ii) LSD-induced behavioral changes outlasted the depression of raphe unit activity; and (iii) raphe neurons were at least as responsive to LSD during tolerance as they were in the nontolerant condition.*

The phenomenological effects of *d*-lysergic acid diethylamide (LSD) and theories concerning the biological bases of its action have had a major impact on psychiatry, psychology, and pharmacology over the past 25 years. A large body of evidence now suggests that brain 5-hydroxytryptamine (serotonin) may play an important role in mediating the dramatic psychobiological effects of LSD (*1, 2*). The most compelling of these data come from electrophysiological studies demonstrating that small quantities of LSD, administered either intravenously or microiontophoretically, markedly depress the discharge rate of serotonin-contain-

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