BOOK REVIEWS

Endogenous Dangers

Stress, the Aging Brain, and the Mechanisms of Neuron Death. ROBERT M. SAPOLSKY. MIT Press, Cambridge, MA, 1992. xii, 429 pp., illus. $55.

The brain is undoubtedly the master controller of the endocrine system. In response to stress, the pituitary releases adrenocorticotropic hormone (ACTH), which triggers the release of glucocorticoid hormones from the adrenal glands. By a feedback action on the brain, glucocorticoids inhibit ACTH release and thereby maintain homeostasis. But do chronic stress, the aging process, and alcohol release glucocorticoids in concentrations that actually damage the brain? The seeds of this question lie in the discovery in 1968 by Bruce McEwen of Rockefeller University that the hippocampus, a brain region intimately involved in short-term memory and known to be unusually vulnerable to a variety of insults, contains many corticosterone receptors.

Stress, the Aging Brain, and the Mechanisms of Neuron Death is a provocative theoretical work from Robert Sapolsky, who was one of McEwen's students. Although the book describes the normal brain/adrenal axis in great detail, it is not a textbook of neuroendocrinology. Rather, it is several detailed and valuable review articles on the brain/adrenal axis, the adrenal hormones in aging, and the known mechanisms of neuronal death. These subjects serve as the springboard for Sapolsky's hypothesis that adrenal hormones not only influence the brain but injure or endanger it when they are released by chronic stress or during the aging process. The hypothesis is based on the following reasoning. First, the hippocampus is a corticosteroid hormone target and known to be injured by anoxia, seizures, and alcohol. Second, since stress, alcohol, and aging release glucocorticoids in excessive amounts (a point about which there is considerable controversy), perhaps glucocorticoid-receptor stimulation is the mechanism by which brain damage occurs in senile dementia, Alzheimer's disease, alcohol neurotoxicity, and other neuropathological conditions.

Writing in a personal and enthusiastic style, Sapolsky conveys devotion to his hypothesis and trepidation at what it portends. If he is correct, it is extremely bad news for the brain. Sapolsky envisions the brain as an organ under constant assault by everything stressful because stress causes the adrenal glands to release corticosteroids in excessive amounts. Given this potential internal mechanism by which the body attacks its own brain, Sapolsky is alarmed by the fact that millions of people are given glucocorticoids for the treatment of arthritis, asthma, and a variety of other disorders. If his "glucocorticoid endangerment hypothesis" is correct, it would seem that the chronic use of glucocorticoids in current medical practice borders on malpractice.

The assertion that chronic stress and glucocorticoids damage the brain irreversibly would be truly alarming if the case for it were not so weak. Sapolsky's hypothesis rests primarily on experimental data from rats and monkeys. The results of the rat experiments, mostly conducted in Sapolsky's laboratory, have been interpreted as demonstrating that glucocorticoids either injure hippocampal neurons directly or decrease the threshold at which the neurons are damaged by other insults. Thus, corticosteroids were reported to exacerbate damage produced by ischemic insult or by the excitatory neurotoxin kainic acid. From these data, Sapolsky has inferred that, to use his metaphor, when some stressful factor pushes a neuron to the edge of a cliff, glucocorticoids push it over. However, the neurotoxic treatments used in his experiments are well known to produce highly variable lesions, and it is very difficult to know whether small differences in damage among animals are due to the variability of the kainate lesion, for example, or are the result of the co-administered glucocorticoids. Unfortunately, Sapolsky's studies have not been rigorously addressed or replicated by other investigators, and there appear to be few or no clear, convincing data from rats establishing that glucocorticoids are either directly or indirectly neurotoxic.

Of central importance to Sapolsky's hypothesis are the data from his primate studies, since regardless of whether or not the rat data make the case, convincing primate data could stand alone. Sapolsky hypothesized that monkeys low in the social hierarchy experience chronic stress and, as a result, should exhibit hippocampal damage. He studied Kenyan vervet monkeys that had been trapped and placed in captivity months or years previously. Terminally ill animals that died spontaneously exhibited ulcers, hyperplastic adrenals, splenic lymphoid depletion, and colitis at autopsy. Upon pathological analysis of immersion-fixed tissue, Sapolsky reported finding hippocampal pyramidal neurons in these animals that were actively degenerating compared with those in healthy monkeys euthanized for other purposes. However, the monkeys that died naturally constituted the experimental group only because they were all found dead in their cages, and the morphological features cited by Sapolsky as evidence of stress-induced hippocampal damage (figure 14.2, p. 312) appear to be typical postmortem degenerative and edematous processing artifacts. If profound hippocampal neuron degeneration (more than 80% of pyramidal cells in some cases) had been occurring in these monkeys in response to socially induced stress during life, as Sapolsky asserts (p. 311), some of the 12 animals examined would be expected to exhibit obvious evidence of long-standing and extensive cell loss, rather than simply dark cells and watery "halos" at autopsy. Although some evidence of cell loss is presented, the lack of methodological detail about cell counting presented in the book and the original report of the work make its significance difficult to determine.

Furthermore, the degree of stress experienced by the monkeys is open to question. Sapolsky states on page 311 that "although we had no behavioral data available, these appeared to have been socially subordinate animals from cages with particularly aggressive dominant individuals." Although the fact that the dead monkeys had numerous bite marks whereas the controls didn't is cited as significant, one is left to wonder whether this is a reliable indicator of social stress endured in life. In fact, in the absence of behavioral data it is unknown whether the control animals endured less stress than the experimental animals. If the question under study is the effect of stress on hippocampal structure, surely stressed and unstressed animals must be distinguished behaviorally and their brains processed under similar conditions.

The other piece of evidence cited in support of Sapolsky's hypothesis comes from his study in normal monkeys in which cortisol pellets were implanted directly into the hippocampus. Notably, after one year of continual exposure, no hippocampal cell loss occurred. However, minor dark-cell changes typical of tissue-processing artifacts are again cited as evidence of neurotoxicity. To accept this, the reader must believe that the acute degenerative process began a year after implantation, just as the monkeys were about to be killed. Sapolsky states that "collectively, these rather grim studies show that sustained and severe stress can damage the primate hippocampus." I think not.

On the basis of what appears to be a weak

case for stress- or glucocorticoid-induced hippocampal neurotoxicity in animals, Sapolsky proceeds to address with alarm the widespread clinical use of glucocorticoids in humans. Although he has concluded that these drugs probably cause irreversible brain damage, the available evidence suggests that the Food and Drug Administration need not halt the clinical use of glucocorticoids immediately. Millions of patients have been treated with large doses of glucocorticoids for decades without evidence of short-term memory impairment. If glucocorticoids were damaging the hippocampus, sustained memory loss would be an expected clinical consequence. That memory loss has not been seen over many years in many patients suggests that hippocampal damage is probably not occurring.

Although Sapolsky may ultimately be proved correct, his hypothesis has so far garnered little experimental support or attention from beyond a small circle of true believers. Given the possibly disastrous long-term consequences to millions of patients receiving glucocorticoids, and to more hundreds of millions of stressed and aging lovers of alcohol, perhaps it is time for previously uninvolved members of the larger neuroscience and medical communities to address the experimental basis for this provocative and alarming hypothesis.

Despite these critical comments, I highly recommend this book for its lucid and meticulously documented presentation of a compelling subject. Those of us who refrain from such bold theorizing should be grateful that the author has presented his testable hypothesis in such a clear and provocative way.

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Vignettes: Biology for the Populace

"Unobtrusive, quiet and retiring, without being shy, humble and homely in its deportment and habits, sober and unpretending in its dress, while still neat and graceful, the dunnock exhibits a pattern which many of a higher grade might imitate, with advantage to themselves and benefit to others through an improved example." With these carefully chosen words, the Reverend F. O. Morris (1856) encouraged his parishioners to emulate the humble life of the dunnock, or hedge sparrow *Prunella modularis*. . . . The Reverend Morris's recommendation turns out to be unfortunate: we now know that the dunnock belies its dull appearance, having bizarre sexual behavior and an extraordinarily variable mating system. Had his congregation followed suit, there would have been chaos in the parish.

—*N. B. Davies*, in *Dunnock Behaviour and Social Evolution* (Oxford University Press)

Recently, while driving home, I switched on the car radio just in time to hear a man declare "I have made an estimate of the cost of sex . . ." This is a long-standing problem in evolutionary theory, of course, so I wondered which of my distinguished academic colleagues was speaking. The voice went on ". . . and it works out at forty pence a go, spreading the cost of a double bed over fifteen years. And I think it is worth it."

—*J. P. W. Young*, in *Genetic Interactions among Microorganisms in the Natural Environment* (Elizabeth M. H. Wellington and Jan D. van Elsas, Eds.; Pergamon Presss)

Botanical Defenses

Plant Resistance to Herbivores and Pathogens. Ecology, Evolution, and Genetics. ROBERT S. FRITZ and ELLEN L. SIMMS, Eds. University of Chicago Press, Chicago, 1992. x, 590 pp., illus. $75; paper, $29.95.

Plant breeders have capitalized on the defenses of plants since the beginning of modern agriculture. To this end, they have explored the genetics of particular resistances, their effectiveness in deterring attack, and the pleiotropic effects of carrying resistance genes. Pick up any volume of *Crop Science* and you will find dozens of papers describing the performance of resistant cultivars; these field trials offer a virtually untapped resource for biologists interested in the ecology and evolution of plant resistance. *Plant Resistance to Herbivores and Pathogens* attempts to meld the approaches and perspectives of agriculturalists and evolutionary ecologists to present a synthetic view of the dynamics of plant-enemy interactions.

Certainly agricultural plots are much simpler than natural systems. The question is, do they differ in too many ways to be of use to the evolutionary ecologist? Kennedy and Barbour's chapter surveys the genetics of crop resistance and raises the possibility that the simple genetics underlying many resistance traits in crops may not be representative of those in natural systems. Without careful genetic analysis, however, it is imprudent to make assumptions about the number of genes contributing to a trait (for a recent review see Orr and Coyne, *Am. Nat.* **140**, 725 [1992]). Agricultural systems are also more homogenous in spatial distribution, phenology, and genotype, and, as is explored in parts 2 and 3 of this book, heterogeneity may play a key role in the ecological and evolutionary dynamics of plant-enemy systems. Unfortunately, we know so little about the genetics and population biology of resistance in natural systems that we can do little more than wonder whether our inferences from crops would be relevant. This presents an obvious dilemma: for agricultural systems to inform us about natural populations, we must first know more about the relevant factors in natural systems. Chapters by Simms and Rausher, by Berenbaum and Zangerl, and by Via provide us with some of the tools necessary to obtain rigorous information on natural systems, and most of the chapters do an excellent job highlighting the gaps in our knowledge. Experimentalists must now explore the differences and similarities between the roles of resistance in managed and natural systems.

Most of the book is devoted to theories and case studies focusing almost exclusively on natural systems. The span of topics includes evolutionary responses of herbivores and pathogens to plant resistance and changes in higher-level trophic interactions. Not surprisingly, emphasis is placed on issues of more concern with respect to natural than to agricultural systems: What is the level of genetic variation for resistance in natural populations? How important are genotype-environment interactions in determining evolutionary responses? Is resistance costly when natural enemies are absent? A few pioneering studies, such as those by Berenbaum *et al.* on wild parsnip (*Evolution* **40**, 1215 [1986]) and Simms and Rausher on morning glory (*Evolution* **43**, 573 [1989]), feature prominently in many chapters, but it is clear that on most issues the theory has far outstripped the data. This is understandable given the difficulties of quantifying resistance, characterizing its genetics, and documenting evolutionary change. As Antonovics states in his concluding chapter, "The obvious but impressive