

were incompatible with standards of sound patient management and could well impede, or even stifle, a line of contemporary scientific inquiry of extraordinary promise.

The meeting did not lead to resolution of any of these difficult matters, but it was successful in affording some of the major stakeholders the opportunity to exchange views and share concerns. I am confident that, with further cooperative effort involving all of the parties, guidelines and regulations can be crafted that will better balance the legitimate private interests of patient confidentiality and informed consent with the compelling public interest in continuing to foster research on human tissue samples.

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Hippocampal Cell Death

In the Research News article "Is hippocampal cell death a myth?" by Ingrid Wickelgren (1 Mar., p. 1229), the relationship between

neuronal number and memory decline in normal human aging is questioned on the basis of evidence from a new method of cell counting (stereology) and its application to research on rats. With that counting method, neuronal number did not distinguish between old rats with poor versus very good memory. Traditional hippocampal neuronal counts (density measures) in humans, on the other hand, have repeatedly shown a correlation with level of verbal memory.

The source of the traditional evidence is temporal lobe epilepsy patients who have undergone unilateral resection of the anterior temporal lobe and hippocampus (often ages 8 to 40 years) for the relief of drug-resistant epilepsy; hippocampal neurons are assumed to be lost because of detrimental consequences of the epilepsy. The effects on memory are asymmetrical; verbal memory level is associated with neuronal counts in the left hippocampus, the side of language lateralization in the human brain. Magnetic resonance imaging (MRI) studies have confirmed the association between laterality of hippocampal neuronal loss and memory. There is no convergent evidence yet for the stereology method, and the conclusion that there is no association between neuronal counts and memory in aging is premature.

The discrepancy between the human

findings and the new counting method reported in Wickelgren's article could stem from several factors: counting methodology (1), kind of experimental subject (2), sensitivity of memory test (3), age (4), or all these factors and others (5). We must await the application of the new method to human subjects who undergo sensitive memory tests before generalizing the findings on rats to the relationship between memory and neuronal cells in the human hippocampus.

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Wickelgren's article was balanced and well written, and raised some highly important questions. Certainly, the work of Mark West

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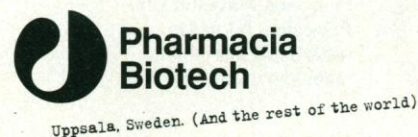
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Peter Rapp, Michela Gallagher, and their colleagues (1) cited in the article is of high quality and has a sound theoretical basis. Nevertheless, there are a number of unresolved experimental issues which suggest that caution is warranted before one reaches the conclusion too quickly that age-related cell death in the hippocampus is a myth.

The negative findings about cell death described in the article were based either on autopsy material or on a different strain of rat from that (F344) usually studied in aging research. In addition, the results are based on quite small samples of subjects (for example, $n =$ five per group) and limited amounts of tissue. The general theory underlying the "new stereology" of the disector and fractionator methods has been clearly validated, but it should be emphasized that, in these specific studies, the analysis relies on a random sampling method that counts very few neurons per subject (100 to 200) within a structure that is not uniform throughout in cell density. Also, the optical fractionator method samples small fractions and relies a great deal on experimental skill, because the investigator or technician who performs the counts must distinguish neurons from glia and keep careful track of which cells have been counted. With this disector method, no photograph-

ic records are available to double-check the counts. The quality of tissue preservation of autopsy material varies enormously, which could influence, among other factors, the ability to evaluate cell type and, consequently, the accuracy of counts. The normal aging changes in hippocampal density previously reported were subtle, being on the order of 20 to 30%. Therefore, tissue variability or small samples, or both, could substantially affect detection of these differences. Rat strains also differ considerably in their rates and patterns of aging; moreover, behavioral performance in a maze, which was used to separate the groups in the study by Rasmussen *et al.* (2), may be influenced by several factors other than cell loss, including dendritic atrophy, synaptic loss, or excitability changes. These are all important technical issues that should be evaluated systematically before the initial results are generalized too widely.

Numerous studies, including several by some authors of this letter, have found aging-related reductions in hippocampal neuronal packing density [see, for example (3)], but studies of hippocampal volume in aging rats (4) have found little evidence of the substantial increases in hippocampal volume that would be needed to account for such density changes if cell loss had not occurred. It

should also be noted that reactive glia and other signs of neuronal damage consistent with cell loss are found in normal hippocampal aging in humans and rats, and West did observe loss of cells in human subiculum, which is closely related to the CA1 field. In addition, one of the primary effects of brain aging appears to be to enhance the *vulnerability* of neurons to other neurotoxic conditions. Thus, aging-related cell loss may not be apparent in all species, strains, or individuals, depending on the other influences present. For example, aging is the major risk factor for the extensive hippocampal neuron loss seen in Alzheimer's disease, suggesting an interaction of aging changes with the neurodegenerative-disease process.

Few in our field think that age-related memory loss depends solely on cell death. Although memory loss is presumably worse after cell death, the death of the cell is generally seen as the final "denouement" of a long phase of declining function (accompanied by memory impairment) during which it is possible that neurons could be "rescued."

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Recent research suggests that loss of hippocampal pyramidal cells may not occur in normal aging, forcing the question as to what *does* change in the aging hippocampus that may underlie age-related benign memory loss. In this context, it is important to note that strong evidence for an alternative to the cell-death explanation has been

known for some time. Studies involving iontophoretic application of neurotransmitters to hippocampal pyramidal cells in aging rats clearly demonstrate reduced responsiveness of these cells to two neurotransmitter agents heavily implicated in memory processes: acetylcholine (1) and met-enkephalin (2). These changes in neural responsiveness with age may be the mechanism behind the "disruption of cells' ability to communicate chemically" that "could underlie a fading memory." The death of the "cell death" hypothesis may give birth to a renewed interest in neural changes such as those that occur in the normal aging hippocampus.

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Corrections and Clarifications

The caption for the illustration accompanying the 17 May Perspective "Stratospheric control of climate" by Alan Roback (p. 972) should have begun, "Surface air temperature anomalies over North America for December 1982 through February 1983."

The ScienceScope section of the issue of 26 April (p. 473) was edited by Jocelyn Kaiser, not Richard Stone, as stated.

In the affiliation given for R. M. Zinkernagel (Letters, 3 May, p. 635), "Universität Zürich" was inadvertently omitted.

Letters to the Editor

Letters may be submitted by e-mail (at science_letters@aaas.org), fax (202-789-4669), or regular mail (*Science*, 1200 New York Avenue, NW, Washington, DC 20005, USA). Letters are not routinely acknowledged. Full addresses, signatures, and daytime phone numbers should be included. Letters should be brief (300 words or less) and may be edited for reasons of clarity or space. They may appear in print and/or on the World Wide Web. Letter writers are not consulted before publication.

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