

mitotic cells of the telencephalon have intrinsic regional properties that foreshadow prospective cytoarchitectonic areas, but does not exclude the role of extrinsic factors in cortical parcellation. In fact, the article cited by Shatz (1) provides the first and, so far, the most dramatic experimental evidence that the border of area 17 can be shifted significantly when the size of geniculocortical input is reduced by prenatal manipulation (1, p. 174 and figure 7). More recently, we confirmed this by showing that the size of thalamocortical input is directly proportional to the size of the cortex (2). Thus, a cortical protomap provides developmental constraints on the outcome of the interplay between cortical cells and their input from extracortical sources. The prefix "proto" in the term "protomap" was introduced to emphasize the primordial, malleable character of the developing cortex. I should not be associated with a strict determination of neural connections, as the phenomenon of initially diffuse thalamocortical projections sharpened by selective elimination was described in my laboratory, followed by experimental evidence that these competitive interactions begin prenatally (3). What I suggested is that the species-specific pattern and cellular characteristics of cytoarchitectonic areas cannot be determined exclusively by extrinsic sources or by neuronal activity and that there must be

some intrinsic regional differences within the embryonic telencephalic wall, including possibly the transient ventricular and subplate zones (4). It is rewarding that the tools of molecular biology are now beginning to supply new lines of evidence for regionally restricted expression of molecules and genes within the telencephalon before or independently of thalamic input (5), thus supporting the basic tenet of the protomap hypothesis. I agree with Shatz that it is an important and challenging subject in developmental neurobiology and that more research needs to be done on both genetic and epigenetic regulation of cortical development.

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REFERENCES AND NOTES

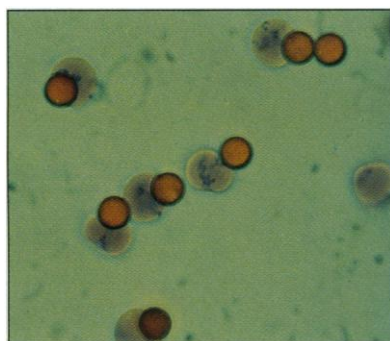
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Protection from Dementia

We wish to comment on the controversy over the role of β -amyloid deposition in Alzheimer's disease (News & Comment, 4 Sept., p. 1336) and particularly the suggestion that glutamate hyperactivity or altered energy metabolism may be a determinant of the extent to which such deposition is harmless. We have evidence (1) that the disease is characterized by glutamate hypoactivity with the capacity for energy metabolism maintained. Thus two abnormalities (excessive glutamate and energy depletion) that can interact with β -amyloid to destroy neurons in culture may not occur in the brain of patients with Alzheimer's. The development of neuroprotective agents will depend on a greater understanding of the function and mismetabolism of amyloid precursor proteins (APP). Processing pathways of APP appear to be affected by a muscarinic agonist (2) and phorbol esters (3) which mimic the transduction pathways of neurotransmitters that use phosphoinositide breakdown as a second messenger. Hence an additional rationale for some transmitter-based therapies is emerging. In Alzheimer's disease circum-

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scribed loss of cortical glutamatergic pyramidal neurons occurs, leading to reduced excitatory input to the remaining cells. This is compounded by reduced excitatory cholinergic modulation. γ -Aminobutyric acid interneurons are preserved, which suggests that inhibitory tone is maintained and perhaps increased. Functional sparing of serotonergic innervation may occur and maintain a negative modulatory effect through serotonin 1A receptors. Therefore, approaches that improve the efficacy of the remaining glutamate transmission may be useful. This improvement may be achieved by action on receptors of cortical pyramidal neurons with agonists (muscarinic receptors), partial agonists (for example, D-cycloserine in the case of N-methyl-D-aspartic acid receptor complexes), or antagonists (serotonin 1A receptors). Drugs that affect transmission are an important goal, as they will be required for most patients if functional disabilities already present are to be improved or reversed. They will also be required for all patients with Alzheimer's disease during the development of prophylactic agents (1).

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The Progress of Science

The instrumentation issue of *Science* (25 Sept.) prompts me to the following thoughts. New machines to power scientific inquiry to higher levels of sensitivity and resolution are detailed to fascinate and excite, but in the end, this tech junkie is left with the sad reality that most of them will be unattainable. Having just completed another masochistic session on a National Institutes of Health Shared Instrument Study Section, I find the contrast between the great opportunities for inquiry afforded by the instruments discussed in *Science* and the

limited funding provided by the government to acquire these expensive tools is remarkable. There can be no doubt that technology is the engine for scientific advance. This is not to demean the importance of a good idea, but it is the quality of the scientific tools that raises the level of the questions and the efficiency of the experimental approach. The lack of a vocal constituency for shared instrument funding has made it the target of choice for removal from the appropriations request menu supplied to Congress. This results in the type of financing strategies that fund five equipment requests from 60 submissions. It should be stated that each instrument grant is usually submitted by from four to ten investigators whose individual research programs would greatly benefit from better analytical tools. Each of those investigators has postdocs and students who would learn these new approaches and then be educated to ask more sophisticated questions about their problems.

Our students and research programs will go on in the absence of such equipment, but the scientific problems we face will not become less complex because of a lack of funds or a commitment to provide the technical means to unravel them.

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