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# TECHNICAL COMMENTS

## Neocortex Development and the Cell Cycle

S. K. McConnell and C. E. Kaznowski report (*1*) that environmental factors can determine the laminar fate of ferret neocortical neurons during the last mitotic division of their ventricular zone precursors. They suggest that the decision of a cortical ventricular zone precursor to generate a deep-layer neuron is made in late S-phase near the transition into G2 of the cell cycle. There is an alternative explanation for the data that is consistent with other findings that suggest a laminar fating of earlier ventricular zone precursors to the neocortex.

McConnell and Kaznowski find that, among migrating neurons, 90% of E29 cells labeled with [$^3$H]thymidine and transplanted 2 hours later into the neonatal host ventricular zone migrate to the superficial (2/3) neocortical layers. However, 90% of these cells transplanted 6 hours later (removed after 4 hours and transplanted 2 hours after that) migrate to the deep (5/6/subplate) layers. Thus, within a 4-hour period near the end of S-phase, 90% of cortical cells must change their laminar fate. If these cells have an S-phase of 8 hours and an unsynchronized cell cycle as stated in (*1*), then only the 25% of the cells that are in the first 2 hours of S-phase and transplanted 2 hours after labeling [rather than the observed 90% in (*1*), figure 2A] should have escaped the deep-layer decision phase in the last 4 hours of S-phase. If the deep-layer decision phase of the cell cycle happened later in S-phase or in G2, then fewer cells transplanted at 6 hours after labeling should have reached the decision phase before transplantation.

Only 20% or less of the transplanted E29 cells actually migrate out of the host ventricular zone into the host neocortical lamina [as detailed by McConnell (*2*)]. It is possible that one of the dissociation, culturing, or transplantation procedures used in (*1*) selected for different 20% subpopulations to migrate among the cells transplanted 2 hours, rather than 6 hours, after labeling. This explanation implies that there were heterogeneous ventricular zone populations among which to select. Heterogeneous ventricular zone populations have been revealed by combining retroviral lineage tracing and [$^3$H]thymidine autoradiography (*3*). In addition, data about cortical genotype ratios in mice produced from blastocyst chimeras have suggested that separate precursor populations may give rise to deep and superficial layer cortical neurons (*4*). We have recently found (*5*) through retroviral lineage tracing of the progeny of individual ventricular zone cells that many mammalian neocortical neuronal clones are restricted to deep, rather than superficial, layers. However, these studies (*3–5*) test for fating or specification of cells, but not if the cells are irreversibly committed to a phenotype; nor do they test whether the commitment can be overcome by environmental cues.

McConnell and Kaznowski also find that most cells lightly labeled with [$^3$H]thymidine (that have presumably divided more than once in the host tissue) migrate to superficial cortical lamina. Once again, these cells may represent a selected subpopulation that is already fated to produce superficial cortical neurons. One would expect continued division by these cells, although the postnatal host tissue environment may artificially limit the total number of divisions by these precursors.

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*Response*: Our experimental design specifically addressed the possibility that the ventricular zone might contain a heterogeneous mixture of precursor cells [reference 20 in (*1*); (*2*)]. Van der Kooy posits that different subpopulations of precommitted cells migrate selectively when transplanted at different times in the cycle. In other words, the postmitotic daughters of committed upper-layer precursors migrate if and only if they are transplanted in S-phase (at 0 hours), and the daughters of committed deep-layer precursors do not migrate when transplanted in S-phase. At later times (4 to 24 hours) the situation would have to reverse: the postmitotic daughters of committed upper-layer precursors never migrate when cells are removed at or after 4 hours after labeling, whereas the postmitotic daughters of committed deep-layer precursors only migrate when removed at or after 4 hours. Such a complex set of rules and behaviors seems a far less likely explanation than a simple change in fate of a single population of cells. However, the possibility of differential selection or survival of precommitted cells is an important problem to address in any transplantation study, so we performed an additional analysis of our data.

Our hypothesis—that S-phase environment determines cell fate—generates an easily examined prediction. If cells are sensitive to environmental determinants in

# Neocortex development and the cell cycle

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