The adult brain is continuously capable of generating new neurons, a process termed neurogenesis, and insults to the brain, such as seizures or injury, can promote the generation of new neurons. Neurogenesis takes place in two major areas of the brain, the subventricular zone and the subgranular zone of the dentate gyrus; in the latter area, new granular neurons are born that can integrate into existing hippocampal circuitry. Are those newly generated neurons good or bad for the brain? It depends. In healthy brain, neurogenesis has generally been associated with improved cognitive performance (1). In addition, newborn neurons can replace cells lost to processes such as aging, and neural cell replacement therapies have triggered much hype for the treatment of neurodegenerative conditions such as Parkinson disease (2). In contrast, the effects of endogenous neurogenesis on epilepsy and its development remain unresolved, and many studies from the past decade have provided conflicting results.

A pro-epileptogenic role of seizure- or injury-induced neurogenesis is supported by findings that granular neurons, born several weeks before or after an epileptogenesis-triggering insult, are characterized by aberrant morphologies and locations; those aberrant neurons were shown to contribute to the recurrent excitatory circuitry within the epileptic dentate gyrus, suggesting that aberrant neurogenesis plays an important role in epileptogenesis (3, 4). In contrast, an antiepileptogenic role of newborn neurons is supported by findings that those cells, when present at their normal locations within the granular cell body layer, are less excitable in epileptic animals compared with controls (5, 6). Mixed results were obtained from studies aimed at preventing epileptogenesis by experimental reduction of neurogenesis (7, 8). The complexity of the influence of newly added cells to existing circuitry was also demonstrated in early neural transplantation studies, in which new neurons transplanted into the hippocampal formation exerted either proconvulsive or anticonvulsive effects depending on the cell source used (9).

To address these conflicting data on benefit or peril of newborn neurons in epileptogenesis, Murphy and colleagues predicted the existence of a heterogeneous population of newborn neurons with some cells being more epileptogenic than others. In the course of their studies, the authors identified a novel type of neuron that comprises only a fraction of all newborn neurons, but which is characterized by a large soma, thick apical dendrites, numerous large basal dendrites, and most important, impressive accumulations of dendritic spines. These studies were based on two transgenic mouse models to track newborn neurons after pilocarpine-induced status epilepticus (SE) and on detailed stereologic analysis of the morphology of newly generated neurons.

In the first transgenic approach, Murphy and colleagues used a Thy1-GFP transgenic mouse in which all dentate granule cells are constitutively labeled by green fluorescent protein (GFP). Animals were injected with 5′-bromodeoxyuridine (BrdU) 1 week prior to induction of SE by pilocarpine in order to label those cells that were born shortly before SE but whose subsequent development and differentiation was subjected to the influence of the SE. BrdU/GFP double-positive cells were identified and characterized in the epileptic animals approximately 3 months following the SE. In the second approach, a double-transgenic mouse was used, in which a GFP reporter...
gene was activated experimentally by induction of a Gli1-CreERT² transgene by exposure of the animals to tamoxifen. With this molecular strategy, reporter gene activation takes place only during the tamoxifen pulse and only in granule cell progenitors, with the result that only the progeny of those progenitors will be labeled permanently by green fluorescence. Here tamoxifen-induction took place 1 week following the SE, and animals were again analyzed after a delay of 3 months.

Using the two independent molecular approaches and different time points of cell labeling (1 week before and 1 week after the SE), Murphy et al. report several important findings. First, in epileptic animals, a large number of adult-generated neurons presented with grossly aberrant morphology. Characteristic aberrant morphologies of dendritic trees were classified as “windswept” and “closed parasol deformation.” Second, most of the adult-generated granule cells that had been exposed to an SE earlier during their development had lost a significant number of their dendritic spines, resulting in reduced spine density and presumably less excitatory input. However, and this is a major new finding, a fraction of about 10% of the adult-generated granule cells was characterized by a greatly increased number of spines, an increase that was apparent not only in comparison to new granule cells in animals exposed to SE, but also compared with normal granule cells of control animals. Third, again, about 10% of the adult-generated granule cells that had been exposed to an SE appeared hypertrophic and were characterized by enlarged somata. Last, increased density and number of spines appeared to be associated with long basal dendrites, and it was those cells that appeared to be in direct physical contact with sprouted mossy fiber cells.

These studies, for the first time, demonstrate the existence of a heterogeneous population of adult-generated granule cells that had been exposed to SE during their development as a possible explanation for the apparent pro- and anti-epileptogenic roles of newborn neurons. Although functional studies were not performed, and cause–effect relationships were not investigated, it is tempting to speculate that the newly identified spiny cell type, which is characterized by high spine densities in juxtaposition to sprouted mossy fibers—even though present only in a 10% fraction of the newborn cells—may receive more excitatory input and may thus contribute significantly to epileptogenesis. For future work, it will be important to validate the present morphologic findings in functional assays and to correlate spine morphology with seizure phenotypes in epileptic animals. The enlarged somata of the spiny cells might be taken as a marker to perform more directed physiological studies to confirm increased excitatory input to those cells. Consequences of the findings from Murphy et al. are far-reaching: if there is a hyper-epileptogenic fraction of newborn neurons, it will be important to determine how these neurons are generated in contrast to the majority of adult-generated neurons. Are they derived from a different subpopulation of neural stem cells, or do these cells receive different environmental seizure-related cues that direct their development? Understanding which cues control differentiation and functional integration of newborn neurons will also be of importance for translational research using neural cell grafts to treat epilepsy (10). If the remaining questions are answered, it might eventually be possible to develop anti-epileptogenic therapeutic strategies to direct the fate of adult-generated or transplanted neurons with the ultimate aim to increase the number of antiepileptogenic neurons and to reduce the number of pro-epileptogenic neurons. It might be time to weed out the spiny trees.

by Detlev Boison, PhD

References
American Epilepsy Society

Epilepsy Currents Journal
Disclosure of Potential Conflicts of Interest

Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.
   Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.
   This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.
   This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (DGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

   Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

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Section #1 Identifying Information

1. Today’s Date: 6/8/2011

2. First Name Detlev Last Name Boison Degree PhD

3. Are you the Main Assigned Author? ☑ Yes ☐ No

   If no, enter your name as co-author:

4. Manuscript/Article Title: After the Storm: From Windswept to Spiny Trees

5. Journal Issue you are submitting for: 11.5

Section #2 The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

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* This means money that your institution received for your efforts on this study.

** Use this section to provide any needed explanation.
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Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add" box. You should report relationships that were present during the 36 months prior to submission.

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* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

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Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

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D  9/8/2011

Thank you for your assistance.
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Page 3