Title
Surprises and revelations in a career in epilepsy research

Author
Schwartzkroin, Philip A

Publication Date
2015-04-01

DOI
10.1016/j.yebeh.2015.01.014

Peer reviewed

AUTHOR QUERY FORM

ELSEVIER	**Journal: YEBEH** **Article Number: 4191**	**Please e-mail or fax your responses and any corrections to:** **Radhakrishnan, M.** **E-mail: Corrections.ESCH@elsevier.spitech.com** **Fax: +1 619 699 6721**

Dear Author,

Please check your proof carefully and mark all corrections at the appropriate place in the proof (e.g., by using on-screen annotation in the PDF file) or compile them in a separate list. Note: if you opt to annotate the file with software other than Adobe Reader then please also highlight the appropriate place in the PDF file. To ensure fast publication of your paper please return your corrections within 48 hours.

For correction or revision of any artwork, please consult http://www.elsevier.com/artworkinstructions.

We were unable to process your file(s) fully electronically and have proceeded by

☐ Scanning (parts of) your article ☐ Rekeying (parts of) your article ☐ Scanning the artwork

Any queries or remarks that have arisen during the processing of your manuscript are listed below and highlighted by flags in the proof. Click on the 'Q' link to go to the location in the proof.

Location in article	Query / Remark: click on the Q link to go Please insert your reply or correction at the corresponding line in the proof
Q1	Your article is registered as a regular item and is being processed for inclusion in a regular issue of the journal. If this is NOT correct and your article belongs to a Special Issue/Collection please contact m.radhakrishnan@elsevier.com immediately prior to returning your corrections.
Q2	The country name "USA" has been inserted for the author's affiliation. Please check, and correct if necessary.
Q3	Please check if the insertion of "through" here is correct, and amend if necessary.
Q4	Please check if the addition of the term "my" before "early years" is appropriate, and amend if necessary.
Q5	As per journal requirement, kindly provide a "Conflict of interest" section. If there is no conflict of interest, please state that. Please check this box if you have no corrections to make to the PDF file. ☐

Thank you for your assistance.

Epilepsy & Behavior xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Reflections on a Career in Epilepsy

Surprises and revelations in a career in epilepsy research

In retrospect, there was really no rationale for finding myself committed to a career in epilepsy research. It was a surprise — and ultimately, a fortunate one. Although I had long assumed that I would be a research scientist and that I would study the brain, I had no particular interest in epilepsy (or, for that matter, no understanding of what epilepsy really was). I was not a clinical investigator. My goal was to be a basic neuroscientist, to understand how we learned and how we remembered — i.e., to understand the basic mechanisms of cognitive behavior. But because of the vagaries of the war in Vietnam (I was a conscientious objector, carrying out alternative service after I received my PhD), I found myself in David Prince's epilepsy laboratory at Stanford University. There I discovered that I could pursue my interests in brain plasticity within the context of studying a clinically important disorder that affected millions of people [1]. [It is somewhat of a puzzle to me why more young scientists who are focused on basic brain mechanisms, and who seek to explore the mysteries of how our brain works, are not drawn to such clinically important lines of study within which they can pursue their basic science interests.]

Over the course of many years, I have been repeatedly surprised to find how many of our choices (and how much of our success) are not really planned but rather a function of being in the right place at the right time. It is perhaps not exactly serendipity, but close. As mentioned above, I virtually fell into David Prince's basement lab and began my epilepsy research career along with such current luminaries as Tim Pedley, Jeff Noebels, Bob Fisher, and Bob Wong. I was later also fortunate to arrive in Per Andersen's Oslo laboratory (as a postdoctoral fellow), just when he was introducing the in vitro slice preparation for neurophysiological research. In Oslo, and later back at Stanford, I was able to help develop that preparation and apply it to questions about seizure/epilepsy mechanisms [2].

Using the slice preparation, my laboratory at the University of Washington subsequently made a number of "discoveries." For example, we found that cellular and synaptic mechanisms in the young/immature brain are not the same as in the adult brain. While this idea now seems rather simplistic, early epilepsy researchers had generally assumed that what underlay seizure activity in the adult was likely to be similar in the baby. More by luck than by intention, our laboratory began to uncover significant differences, particularly in the nature of immature GABAergic inhibition [3]. The focus on inhibition subsequently led to our studies of interneurons and their direct (and indirect) synaptic connection to pyramidal cells in the hippocampus [4].

When I started working in the epilepsy field, our expectation was that we would solve the mysteries of epilepsy within the next 10 or 20 years — certainly before I retired. It was a time of terrific progress, both conceptually and technically. Using newfound neurophysiological sophistication (the basis for defining the epilepsies), we could now focus on the single cell and synaptic levels as never before. And yet here we are, 40 years later, still struggling with many of the same questions. And still unable to cure these diseases — or even treat them adequately in many people. The problems are much harder than they seem. Today, also a time of tremendous advances, I continue to feel optimistic that we are on the verge of significant breakthroughs.

Part of this optimism is due to the powerful technical approaches currently in the epilepsy researcher's (and clinician's) arsenal, making it possible to understand more clearly the basis of the epilepsy diseases. In this respect, it has become clear to me that technology really does drive the science. Our enhanced conceptual understanding of different types of epilepsy and our (at least theoretical) ability to treat each form of the disease according to its underlying mechanism (i.e., rational therapy) have been consequences of advances in such technologies as imaging, genetics, and molecular biology. And for the laboratory epilepsy researcher, these developing technologies have allowed us to identify/develop and characterize appropriate animal models, a critical step toward clinically relevant experimentation [5].

As a student, I had a somewhat romantic and idealized picture of research activity — carried out by a dedicated individual working diligently in his tower (or basement), to emerge occasionally to publish a paper or attend a conference. I soon discovered that research was anything but a lonely enterprise, that it is essentially social and interactive. And it has become even more so in the current research environment. With very few exceptions (and none that I can think of in the epilepsy research field), progress is dependent on sharing and mutual support. For example, although I am basically a cellular neurophysiologist, it is hard for me to imagine my research program without the contributions of neuroanatomist partners (a special thanks to Jurgen Wenzel), molecular biologist collaborators, and clinical colleagues [6]. This social feature of the field is one of its great rewards. The friends I have made, and the colleagues with whom I have worked, have enriched my experience of scientific investigation beyond measure.

The social feature of research is closely tied to our sense of history. In science in general, and in epilepsy research in particular, we have had an awareness that current progress builds upon the work of those who came before us. It is a real pleasure to feel part of a long arc of effort, to trace my scientific lineage back through generations, through my teachers and mentors, to those who pioneered neuroscience and epilepsy research. This sense of history, surprisingly, seems to be evaporating in recent years. Perhaps because young researchers are overwhelmed by the amount of new information available, most seem to have little concept of what was contributed 20, 50, or 100 years ago. One can only wonder, therefore, how many times we might reinvent the wheel.

One extraordinarily important and pleasant surprise for me was the experience of training students and fellows. I knew from early in my career that I was not cut out to be a lecturer and so did not think of myself as a "teacher." But although I avoided the formal lecture format,

http://dx.doi.org/10.1016/j.yebeh.2015.01.014
1525-5050/

I discovered that as a mentor in the laboratory, I had something valuable to offer my students. This type of teaching experience was tremendously gratifying. I am particularly grateful to all those students, fellows, and young investigators who went through my laboratory. Many of them – people like Mike Haglund, Carl Stafstrom, Damir Janigro, J-C Lacaille, Helen Scharfman, Paul Buckmaster, Scott Baraban, Catherine Woolley, and Jong Rho – are now themselves leaders in our field. They are the most important legacy I can leave to epilepsy research.

Q4 One of my expectations in my early years was that there would be sufficient resources in the epilepsy research field to support all comers. Thus, when my students failed to get a grant funded or a paper published, I could provide encouragement by telling them that if they worked hard and produced good work, there would always be a job opportunity awaiting them and grant funding to support their efforts. As years went by, it became more difficult to provide that assurance. Much to my surprise, it seemed no longer a sure thing that the system would reward hard work and excellent thinking with substantive rewards. Colleagues would sometimes complain to me about how "political" the system seemed to be – that success depended on who you knew and your ability (not related to scientific excellence) to find a way to the "inside." While I used to argue against that line of thought, it became more and more difficult to do so as the field became larger and the competition for limited resources became greater.

Perhaps as a result of this experience, I have learned that there are several ways one can contribute to the epilepsy research enterprise. There is, of course, the work done in the laboratory. The epilepsy researcher's goal is to discover something that will ultimately help the patient with epilepsy. But it turns out that this goal is only occasionally realized. Then, there is the classroom (in the broadest sense), with opportunities to train another generation of researchers who may – especially if you do not – make the next critical discovery. Another contributory pathway that I have found satisfying is as an editor of published material [7]. As they say, "If you don't publish it, you may as well have never done the experiment." Given that truth, editors and journals have a critical place in the research arena.

Over the course of almost 40 years, an important part of my identity has been "epilepsy researcher." It has been a wonderful ride, with many rewards. And it is now time to step aside and make room for the next generation. Q5

References

[1] Schwartzkroin PA. Mechanisms of brain plasticity: from normal brain function to pathology. In: JJr Engel, Schwartzkroin PA, Moshé SL, Lowenstein DH, editors. Brain plasticity and epilepsy: a tribute to Frank Morrell. San Diego: Academic Press; 2000. p. 1–15 [Int.Rev.Neurobiol. 45:1–15].

[2] Schwartzkroin PA, Prince DA. Cellular and field potential properties of epileptogenic hippocampal slices. Brain Res 1978;147:117–30.

[3] Mueller AL, Taube JS, Schwartzkroin PA. Development of hyperpolarizing inhibitory postsynaptic potentials and hyperpolarizing response to GABA in rabbit hippocampus in vitro. J Neurosci 1984;4:860–7.

[4] Knowles WD, Schwartzkroin PA. Local circuit interactions in hippocampal brain slices. J Neurosci 1981;1:318–22.

[5] Pitkanen A, Schwartzkroin PA, Moshé SL, editors. Models of seizures and epilepsy. San Diego: Elsevier; 2006.

[6] Wenzel HJ, Schwartzkroin PA. Morphological abnormalities associated with genetic epilepsies. In: Schwartzkroin PA, editor. Encyclopedia of basic epilepsy research. London: Elsevier; 2009. p. 1366–73.

[7] Schwartzkroin PA (Editor-in-Chief). Encyclopedia of basic epilepsy research (3 volume set), Academic Press/Elsevier, Oxford, UK; 2009.

Philip A. Schwartzkroin

Department of Neurological Surgery, University of California at Davis, USA Q2

Tel.: +1 530 754 5029.

E-mail address: paschwartzkroin@ucdavis.edu.

9 January 2015

Available online xxxx

Please cite this article as: Schwartzkroin PA, Surprises and revelations in a career in epilepsy research, Epilepsy Behav (2015), http://dx.doi.org/10.1016/j.yebeh.2015.01.014