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Eric Kandel: a life in learning and memory

Interviewed by Steve Carney

Do you think it is easier to be starting a career in science now than maybe 50 years ago?
Actually it is much more difficult. It was much easier in my day – there was more funding and almost any person who was at all competent didn't have to worry about funding. There are more people in science now and it is much more competitive, the reviewing bodies, with the exception of the Howard Hughes Medical Institute, are very cautious. Before you get supported for a particular project, you have to show that you are able to do it – which is a bit ridiculous. So it is much more difficult today.

'The issue is more of funding the field than accessibility of colleagues and advice'

You have commented that at the NIH you were given the opportunity to explore science in the knowledge that there were always experienced people to help. Do you think this attitude and framework still prevails?
That's right! That's even more true now because the field is more structured. When I came along there were no textbooks in the field that were really useful and the number of people doing neurobiology was small. Now there are lots of people that can help you. The issue is more of funding the field than accessibility of colleagues and advice.

Eric Kandel
Center for Neurobiology and Behavior

Eric Kandel was born in 1929 in Vienna and moved to the USA in 1939, shortly before the outbreak of World War II. His interest in psychoanalysis developed while studying at Harvard, but in order to practice in this field he qualified in medicine and specialized in psychiatry, qualifying in 1956 from New York University Medical School. In 1955, he took an elective period with Harry Grundfest, sparking his interest in neurobiology. During a productive period at the National Institutes of Health (NIH), Kandel effectively began his lifelong study into the neurobiology of learning and memory. Leaving the NIH in 1960 for a psychiatric residency at Harvard introduced him to Stephen Kuffler and his research group. This allowed Kandel to remain engaged in neurobiology and allowed the active planning of his future studies on learning and memory in the giant sea snail, *Aplysia*. After brief, yet productive, appointments in Paris (France) and once again at Harvard, Kandel took a position at New York University and was later appointed founding Director of the Center for Neurobiology and Behavior at Columbia University. Professor Kandel has been honored many times, perhaps most notably with the Albert Lasker Prize in 1983, and of course the Nobel Prize, which he shared with Arvid Carlsson and Paul Greengard in 2000.

Isaac Newton once famously said: 'If I have seen further it is by standing on the shoulders of giants'. Who would those giants be for you and why?
There is no question that I was tremendously influenced by giants. Bernard Katz is probably the person who influenced me particularly, because he opened up the modern study of synaptic transmission on the cellular level. Stephen Kuffler, who developed the Neurobiology group at Harvard, influenced me in terms of an attitude to enzymes and how to develop a Neuroscience group at Columbia; Eccles for his enthusiasm about the study of the brain and my own mentor Dominick Purpura and Harry Grundfest because they got me going in science.

'The best piece of advice that I ever received is to ignore lots of advice'

Could you outline the aspects of your research that gave you the most satisfaction?
I think developing *Aplysia* as a model system for learning and memory was extremely satisfying, for it was by no means clear at the beginning that it would turn out to be as productive and as generalizable as it has been. But it has turned out to be extremely useful and I got a lot of pleasure out of that.

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Some specific discoveries that came out of the system included: the ability to show that learning produces its changes by altering the strength of specific synaptic connections; that long term memory differs from short term memory in requiring transcription – that you need to turn genes on; that CREB was a major regulator of transcription; that in order to turn CREB on, you needed to remove a repressor (CREB-2) and that long term memory differs from short term memory in requiring the growth of new synaptic connections. I would say that in *Aplysia* those were the most important findings and also in showing that some of these principles apply to the mouse and to more complex forms of learning.

'You've got to follow your own nose in science'

What was the best piece of advice you ever received?

How do you answer a question like that? I think the best piece of advice that I ever received is to ignore lots of advice and to do what you think is the correct thing to do in science. I don't mean from a moral point of view, but from the point of view of judgment. Many times I made discoveries from following a particular path. Eccles discouraged me from going into *Aplysia*, other people discouraged me from going from *Aplysia* into the mouse. But you've got to follow your own nose in science, you cannot be too readily influenced by other people's ideas of what you should do.

What do you see as the major problems that need to be addressed to allow the development of future psychiatric blockbuster drugs?

What was useful in memory loss was that there were very good animal models. There are not, at the moment, very good animal models of depression or schizophrenia, although people are beginning to work on that. So I think that trying to identify some of the critical genes involved in depression, schizophrenia and anxiety and using those to generate mice that have those defects will be a very important step.

If you were successful with the drugs that are being developed at the moment, what would your endpoints for success be? Would it be to reverse memory loss or just to retain it at a certain level?

I think that it would be very good in the beginning if we had a very good drug that was able to improve memory to a modest amount or degree. But obviously, the better it was, the more thrilled one would be, but since there is really nothing out there that is terribly useful at the moment, I think we would be grateful for any step forward.

Do you think that fundamentally it is possible to restore memory?

Yes. To restore memory – one can regain the function of memory back to a fairly good level of proficiency, but I don't think that any memories that have been lost before drug treatment had begun will come back. So it will help you acquire new memories once you start the drug but it will not necessarily help you with memories that you have not been able to store once you have had the onset of age-related memory loss.

'I found the Nobel Prize to be a stimulus to do bigger and better science'

Winning the Nobel Prize would be seen by many as the pinnacle of a scientist's career. How did it feel for you – was it a motivating experience or did it leave you with the feeling that you had achieved everything in science?

I don't think that most people who do science seriously ever think they have achieved everything. Science is such an immense undertaking, there are an almost unending series of questions that unfold in front of one. As such science is so refreshing and invigorating, rather in fact I found the Nobel Prize to be a stimulus to do bigger and better science.

When you started, you chose a field that was particularly challenging, if you were starting off in science now, what fields other than learning and memory do you think would pose similar levels of challenge now?

One problem would be a molecular approach to sociobiology, the study of molecules that lead to social behavior. Another would be the molecular mechanism of attention. Trying to see whether we can develop imaging techniques to measure the outcome of psychotherapy. I mean, there are a whole bunch of problems that interest me, that I'm probably not going to tackle, but that fascinate me. The issue is not that problems are not out there, there are lots of fascinating problems. In terms of learning and memory there are the relatively untouched areas around the boundaries of psychology and neuroscience. So the borderline would be somewhere that would captivate my interest. The issue for young people, primarily, is the assurance that they can get funding to carry out difficult projects. As long as funding is so conservative, people are going to take one tiny step forward and one tiny step back – they are not going to take on bold challenges and that's the sadness of the current situation.

How do you think you might change that?

I think that people should realize the benefit that comes to society from having powerful science – look what a wonderful society we have in England and the USA, for example, because of science. That should come from the Presidential level. Although I must say, California shows it can be done on a state level as well. They had a referendum on Stem Cells, which has been very influential, so maybe it can be done on all levels, but certainly it needs to be at the level of the national Government. This would be the most effective.

'I'm not a methodologist, I'm a consumer of methodology'

Do you think that people worldwide have a sufficiently high opinion of science and scientists in the public eye?

By and large they are very suspicious of scientists. It varies of course, many people respect scientists and respect the work that they do, but people have the feeling that scientists want to control the human mind. Certainly religious groups have been very much concerned about the moral consequences of science.

When you realized that modification in synaptic connections were responsible for memory, at the time did you feel that investigations into elucidation of this mechanism were likely to be fruitful?

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Of course. If you look at my science it actually looks more planned than it was. But at each step I realized that the next step would be quite fascinating and, scientifically, quite important.

Were there technological barriers that hindered progress at the time?
Quite the opposite. As I moved along, my career was helped at almost every point by scientific developments made by others. The development of biochemistry at the single cell level opened up the study of nerve cells, the development of molecular biology and the development of morphological techniques to follow on-line development of new synaptic connections. Most of those things were adopted by me from other people's pioneering methodological efforts – I'm not a methodologist, I'm a consumer of methodology. Most of the good methodologies are easy to learn. I think you need good colleagues who are willing to help you, or good collaborators that you can join forces with. But that has been terrific in US science, in fact, I would say in international science.

'I think the next 10 years are going to be magical years for psychiatry'

How difficult was it to convince the scientific world that such investigation could be achieved using invertebrate models?
I should distinguish between two things: one is on the level of my peers, and the other at the level of funding. I never, for a moment, had difficulty, in terms of my funding because I was working on *Aplysia*. People, I think, assumed that I was a serious, competent scientist and since I came from psychiatry, they realized that I was interested in the human mind, even though I was working in the snail. But within the scientific community, and particularly the psychological community, the question was: how much could you learn about mental processes by looking at an invertebrate? There were ethologists who thought, 'My God, behavior is conserved, just like morphological structure is conserved'. But there weren't many behaviorists or cognitive psychologists who thought 'he can't do that, it's just too simple, the rules are going to be very different'.

What do you think about Systems Biology? Do you think that's an area that can be exploited to develop psychiatric medicine?
Absolutely. I think the next 10 years are going to be magical years for psychiatry, we are going to benefit enormously from molecular neuroscience and systems neuroscience. You are absolutely right. I think you could model complex aspects of the visual system, of olfaction, of the touch system. So you could take sensory systems and get a good idea how the various stages operate. We're really recruiting fairly heavily in computational neuroscience at Columbia. We've recruited three outstanding people over the last several years to develop a unit in this area, because we think it's so important.

Do you think the field of learning and memory is particularly amenable to a Systems Biology approach because the molecular players in the process are reasonably well known and understood?
That's an interesting idea. It may be. We can certainly take simple systems and model them quite usefully. I think one could have the simulation of reflexes and all the molecular components involved. I think people like Jack Byrne and Larry Abbott are beginning to do that.

Do you think that the re are any psychiatric diseases that will not be amenable to treatment in the future? Which ones and why?
Oh gosh. You know, I think the most troublesome ones are the mental retardations, but even they may be able to be tackled with amniocentesis. Since a lot of these are genetically determined, we should be able to screen out with appropriate genetic tests, whether or not a particular fetus is likely to have mental retardation and give the mother the choice of a termination. I think those are the most challenging: genetically determined mental retardations are very difficult diseases to address.

Presumably, these would not be targets that you would imagine would be taken up by the Pharmaceutical Industry. But do you think that in autism, for example, where there may be an initial developmental problem, it may be possible to produce drugs capable of addressing the disease?
That would be an important disease to make progress on because it seems to be becoming a bit of an epidemic, it's increasing in frequency and it's an extremely disabling disease. One knows relatively little about it but there are some genes being identified that seem to be critical for it, neuroligin being a specifically important one.

What challenges and what satisfaction have you derived from your involvement with Memory Pharmaceuticals?
I must say that it has been quite an exhilarating experience to see something that you sought in the lab being in clinical trials. It is wonderful to think of a company over dinner and then show up a couple of years later and find there is a building (not that we own it, but we rent it) employing 70 people carrying out extremely interesting and high quality science. It is very satisfying. It is really a very, very good group.

'You have to give some things up – you can't dance at all the weddings'

Do you spend any time at the bench now?
I spend no time working directly at the bench myself. I walk around and I spend time with the people doing the science, but I, myself, don't work with my hands. You know, I think there is so much excitement in just speaking to the people and discussing experiments with them and evaluating data that I don't feel compelled to do them myself. Sitting in a neurophysiology experiment still thrills me and I like to try something every once in a while, but it's not a major preoccupation. I think one has to realize, that as one moves through various phases of their career, in order to take on some additional things, you have to give some things up – you can't dance at all the weddings.

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