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Interview date: September 15, 2015
Interviewer: Hank Grasso

Hank Grasso: Recording.

HG: The first thing we wanted to talk about was the early influences that directed your career path.

De-Maw Chuang: Okay. I think there are several people who really influenced my career path. The first one is probably my dad, who just passed away last month, at the age of 99. He encouraged me to go abroad to study to conduct research to benefit the human being, instead of keeping me around him to take care of him. I would say he had tremendous vision. That's the first person who influenced me. I would give credit to my Ph.D. thesis adviser, Melvin Simpson. He was my first teacher in the United States. Then, I did my postdoc with Dr. Herbert Weissbach, who is a National Academy of Science member. He encouraged me to come to NIH. He said "NIH is a great place to work," and encouraged me to come here instead of going to universities. And that was a correct decision.

The next person, I would say, is Erminio Costa. I worked with him for 13 years. He was the Chief of the Pre-clinical Pharmacology and it was during that period that I became a neuroscientist.

HG: I am going to ask that we do take the glasses off. I'm losing your eyes to two very large glares. I'm sorry. I don't know how to correct for that. Sometimes there's a spray, a mist or something. If I could ask you to repeat those early influences. Thank you.

DMC: There are several persons who affected my career path in the early days. The first person I would like to acknowledge is my late father, who passed away last month at the age of 99, because he encouraged me to come to the United States after I graduated from the university. His vision was that I should come here to get the best training as a scientist to benefit human being. So he had a great vision. Then the next person I would like to bring

up is my PhD thesis advisor, Dr. Melvin Simpson. He really gave me tremendous guidance for my career at the later time.

Then I would also like to acknowledge my post-doctoral mentor Dr. Herbert Weissbach, who is a National Academy of Science member, because he not only gave me good mentoring, but also encouraged me to come to the NIH to advance my career. That was really a very important advice and also a decision that I think I made very correctly. Perhaps, the last person I would like to mention is Dr. Erminio Costa who was my lab chief of the NIMH at St. Elizabeth's Hospital at that time. He was the Chief of Pre-clinical Pharmacology. I think I learned a lot from him during the 13 years that we worked together and it was during this time that I became a pharmacologist and a neuroscientist. These are the persons I would like to acknowledge.

HG: Now how did you find your way to the NIH campus, and then your specialization with lithium? How did you find that pathway?

DMC: This is a very interesting question. Actually I have to first say that I worked at NIMH at St. Elizabeth's Hospital, a mental institution, for 13 years. Then, I moved to the main campus and at that time I was assigned to Dr. Robert Post's branch that's called Biological Psychiatry Branch. He is a world expert on bipolar disorder and, as you know, lithium is a primary drug used to treat bipolar illness. He also studied valproate and carbamazepine as a treatment for bipolar disorder. In that enriched environment, I became interested in the mechanisms of action of mood stabilizers including lithium, valproate, lamotrigine, and carbamazepine, etc.

And I had been very fortunate to have many outstanding young investigators working with me. I have to thank all the wonderful work they have done for me. If I had accomplished anything, I would give all my credits to these young investigators. One particular person I would like to mention is Shigeyuki Nonaka from Japan. At that time he did not yet have a Ph.D. and he came from a pharmaceutical company called Ono. He brought his own money to conduct research in my laboratory and was the key force discovering that lithium has a very strong neuro-protective effect. That was the foundation for the work that I conducted since then, since 1998. In that year, he published three papers about the neuro-protective effect of lithium in the cellular model against glutamate excitotoxicity and in the animal stroke model. And many people said that these three papers changed the field, changed the direction of lithium. It

certainly changed the direction of my laboratory and so I'm very grateful to Dr. Nonaka. He then became a doctor because of work done at NIH.

HG: We talk a lot about collaboration across academic discipline or among institutions. In your own investigations are there some examples of collaboration?

DMC: Yes. I think one of the most exciting things to be in the NIH campus in the opportunity to have interdisciplinary collaboration. NIH is such a great place, as you know. It has 21 institutes and six centers. Just in the main campus alone, we have about 15-16,000 workers. So we have tremendous opportunities to interact with investigators with different backgrounds and have wonderful seminars. We have NIH research festival and have excellent co-facilities. This is a heaven for collaboration. And in my own experience I collaborated with many, many investigators. In the earlier days, I collaborated with Erminio Costa, Richard Wyatt, Steven Paul, Robert Post, Michael Rogawski and Tom Chase. This has been a fantastic experience to have this intramural collaboration. Of course, we are also encouraged to collaborate with extramural researchers, which I did. Also I benefited a lot from these intramural and extramural collaborations.

HG: Is there something that is unique about being part of a government research community or being an NIH scientist?

DMC: Yes, I would say that there are many unique features being in NIH campus. First of all, this is a government institution and, fortunately, we have intramural funds; so we don't have to spend a lot of time writing grant proposals. NIH has been very generous in supporting the intramural researchers. This is a very rich environment. You can interact with not only basic but also clinical investigators. So, there is a lot of cross-fertilization between basic and clinical researchers. We have the opportunity to conduct translational research right away when we have some important findings.

Also, NIH has a lot of core-facilities which really facilitate the progress of research. Another thing is that NIH has an excellent program to attract young investigators. As you can see in the campus, there are many international young investigators who contribute greatly to the research progress. In my own case, as I just mentioned earlier, Shigeyuki Nonaka was from Japan.

HG: Is there an opportunity to use costly equipment that you could not have access to in other kinds of places? Has any of that affected your work specifically?

DMC: There are many core facilities available. For example, in the NIH, NIMH we have about 10 different cores so we don't really need to purchase very expensive equipment. In fact, probably we cannot afford to purchase them anyway, but the core facility, yes. For example we have the best confocal microscopy. We have the best brain imaging facility and the capacity to generate transgenic animals for researchers. And so on and so on.

HG: Perfect thank you. Has there ever been a moment where working here was the most exciting but also the most frustrating? Was there a moment in your career that was…

DMC: Perhaps I can say this. Sometimes you got the most exciting data, but you're not sure whether this is real or not. Whether this is replicable or not. So, you have to do it again. Sometimes, the situation just doesn't allow you to do the experiment right away because of certain limitations or because to generate new data takes a long time. That was a moment that we were very anxious and could be frustrated because we wanted to know whether the important finding we had just made was real or not.

HG: If you could describe one moment of discovery, if there was one that you wanted, that you could talk about that was just that breakthrough moment when the light went on, when you connected the information to realize that something significant happened, what would that moment be?

DMC: Yes. Perhaps I can give an example that happened in the mid-70s when I was a young investigator. The project was to see whether a receptor for neurotransmitters can be internalized into the cell after persistent stimulation of the receptor. That was the question. We then prepared the cells that contained this particular receptor, stimulated them for a long time, and then prepared the soluble and insoluble fractions because our assumption was that when a receptor was internalized, it becomes soluble. It's no longer bound to the membrane.

So we looked at the receptor in the soluble fraction and looked at the receptor binding capacity. I remember I was in my early 30s and I was standing in front of a scintillation counter looking at the numbers and suddenly the number went up, meaning that, yes, in the soluble fraction we could detect a receptor after persistent stimulation. That was a moment that I will never forget. At that time my heart was pumping very hard.

HG: You knew immediately that was significant.

DMC: Right. However, it took years to know its significance because that was beta-adrenergic receptors that we were looking at. About three or four years later, it was confirmed by the group of Dr. Robert Lefkowitz, who won Nobel Prize a few years ago. Years later, it was found that this phenomenon of receptor internalization can occur in almost every neurotransmitter system and has strong implication about receptor desensitization, receptor trafficking and drug resistance.

HG: Was there ever a moment when you were very discouraged? When the things that you….. Well actually I guess I'm wondering about how your question changed over time. The research question that was the center of your work. Did that transition over time and change or has the basic question remained the same?

DMC: Yes. I think the question changed with time. One of the great things to be in NIH is that we don't have to write a grant proposal. So we have freedom to do some pilot experiments and to test whether the hypothesis we put forth was correct or not. As a result, my research always involved some testing and then proving the hypothesis. Once we have established a system, then we move to another project with a different hypothesis. That I would say is an assumption that the extramural people cannot easily do.

HG: If you were looking at a timeline and trying to position your research in the middle of this timeline, who would be the people that you would see as precursors to your own work or stepping stones on the way to your lithium work?

DMC: Right. I would probably mention a few names because in my 42 years in NIH, I think I have had about five or six most important discoveries. When I just came to the Preclinical Pharmacology Laboratory at St. Elizabeths Hospital with Erminio Costa, I was working on a project called tyrosine hydroxylase. It is the key enzyme involved in catecholamine biosynthesis. Actually, our system was adapted from the research conducted by Julius Axelrod. Julius Axelrod, as you know, is a Nobel Laureate of the NIMH and he has already demonstrated the phenomenon of trans-synaptic induction of tyrosine hydroxylase. Basically that was the system we used.

We actually put the animals in the cold, like four degree Celsius, when their bodies get wet so they have cold stress. This increases neurotransmitter transmission and induces tyrosine hydroxylase. We used the system established by Julius Axelrod to demonstrate that this induction process involved the increase of cyclic AMP and activation of the protein kinase A, nuclear translocation of the protein kinase A to activate the biosynthesis of the messenger RNA for tyrosine hydroxylase. This is a good example that our work actually was facilitated by a previous discovery. This is one example.

About the beta-adrenergic receptor I have to give the credit to Dr. Robert Lefkowitz, who won Nobel Prize just a few years ago, because we used his system of frog erythrocyte which is an excellent source for beta-adrenergic receptor. Using his paradigm, we discovered beta-adrenergic receptor internalization.

And the next person I would like to acknowledge is Dr. Robert Post. As I mentioned earlier, he is a world expert in bipolar disorder. Being in his Branch, I became interested in the neurobiology of mood stabilizers.

Perhaps, I can mention another name because I think I have been indirectly influenced by him. This person is Dr. Bernard B. Brodie. He is very famous and was the father of modern neuropharmacology. He worked in NIH in the 60s and early 70s. He won a Lasker award for his research on norepinephrine and serotonin and the understanding of brain function. Because he was a great educator, he trained so many, so many important neuro-pharmacologists; it is countless. He was really someone very special. Julius Axelrod and Erminio Costa, my former boss, were trained by him. My life has been influenced by Erminio Costa. So, I think I am, probably you can say, the second generation of B. B. Brodie’s trainee.

HG: Looking forward are there principal investigators or researchers who are building on your work and taking it in a different direction perhaps?

DMC: I would say that our lithium and valproate studies probably have made significant impact in my view because people picked up our finding of the neuro-protective effect of lithium and also valproic acid and looked at their effect in many pre-clinical models of diseases. Indeed, they not only confirmed my work, but also expanded our work to show that both drugs have tremendous neuro-protective effect in a wide variety of animal models of diseases. We show this in the stroke model, in the Huntington's

disease model, and in the depression animal model, but people have expanded and find that they also work for example in Alzheimer's disease model, Parkinson's disease model, spinal cord injury model, traumatic brain injury model, fragile X model. This actually was conducted by Dr. Carolyn Smith in our institute in building 10, so on and so on. I am very pleased that these findings have been expanded. In fact in some clinical trial have been done and there are some indications that valproic acid, a mood stabilizer, indeed has beneficial effects in patients with stroke and in patients with spinocerebellar ataxia called SCA3.

HG: I'm aware of the lithium protective quality. That is one very significant contribution of yours. You mentioned that there are about five that you think of as your most significant. Would you be willing to explain each of those?

DMC: I would say that the first one is probably my work on trans-synaptic induction of tyrosine hydroxylase. We demonstrated that cyclic AMP is important in the subsequent activation of protein kinase A and nuclear translocation to increase transcription. These are all very important mechanisms for the induction. Actually, these led to the discovery of the important transcription factor called CREB [cAMP response element-binding protein]. That was the first one.

Then, I also worked with some young investigators to demonstrate the recognition site for antidepressant drugs. We were also one of the first to put forth the idea that depression could be the result of improper interaction or balance between the norepinephrine and the serotonin neurotransmitter systems.

Perhaps the next one is about phosphoinositide metabolism. This work actually was facilitated by Michael Berridge in Cambridge University in England. He had a very interesting hypothesis that lithium may work by inhibiting excessive phosphoinositide metabolism in the brain. The theory, which we still don't know whether is correct or not, did inspire me to get into this system. Our study with a whole bunch of young investigators in the NIMH led to the discovery that some glutamate receptors can be linked to phosphoinositide metabolism and this led to the discovery a few years later that there is a so-called metabotropic glutamate receptor.

Another finding is about an enzyme called GAPDH. It stands for glyceraldehyde-3-phosphate dehydrogenase. This enzyme was thought to be a housekeeping gene, but we proved that this was not correct. It

actually has an important role in the neuronal apoptosis and neurodegeneration. After over-expression of GAPDH and nuclear translocation, you can damage the cell, particularly a neuron. This is an important contributor for neurodegenerative and neuropsychiatric disorders.

Lastly is about lithium and valproic acid, which have been the focus of our lab's research for the last 15 years or so. Still there is a lot of work to be done, but we are excited about the progress. We think that lithium and valproate have tremendous translational potential for a number of brain disorders in addition to just bipolar disorder.

HG: Oh boy. That's pretty huge. My God. Has any of your early work ever been reinterpreted or thoughts changed on accepted conclusions?

DMC: Yes, I would say that one good example may be about our study on tyrosine hydroxylase induction. At that time we proposed that cyclic AMP increase always preceded the induction of tyrosine hydroxylase and is essential for the induction of this enzyme. There was a group in Sweden who challenged our result. He said, "No, it's not essential and can be disassociated from the induction of this enzyme, tyrosine hydroxylase." Our group, led by Dr. Erminio Costa and this Sweden group had a lot of exchange and a lot of challenge in the papers and meetings as well. That was a pretty exciting time.

HG: What would you say, what advice or what wisdom would you share for new arrivals, for young investigators, scientists, or researchers? What would be your words of wisdom?

DMC: I always encourage young investigators, who just came to NIH, not to spend all their time in the laboratory. I think they should take advantage of opportunity that they have in NIH to expose themselves to get the best training, to meet with investigators with different background, to collaborate with people. I have seven “C”, capital C, to give to the young investigators. The first one is *Commitment*, meaning that you need to not only work hard. You have to like what you are doing. You have to like research otherwise you cannot do well in research. The second one is *Communication*. You need to talk to people. You need to meet important people. You have to establish a good network. The third one is *Collaboration*. I think the communication should turn into products. The best way to get product is to collaborate with people because you can learn different expertise through collaboration. You can improve the quality of

your research and your publications. Collaboration is really a mutually benefited experience. If you look at a paper in Science and Nature, you can see that it involves a lot of authors from different institutions. The fourth one is to have *Creativity*, because you don't want to do things that have been done by other people. You don't want to just confirm some other people's work. You want to have something that is novel, new and important. You need to select a very creative project. The number five is *Cohesion*, meaning that when you are a young investigator you cannot afford to have too many projects because you just don't have so much energy. You need to focus on some project and do very well in this area such that people can recognize your accomplishment. In other words, you need to have focus. When you are a young investigator you cannot afford to have too many projects to dilute your effort. Number six is *Courage*, meaning that you can probably afford to take some high-risk projects, because high-risk project, although it's hard, often is high payoff. So don't be afraid to take high-risk project. Number seven, the last one, is *Candor*, meaning that you need to follow all the ethical rules. You need to be a good citizen in the research community no matter where you are because you need to have a good reputation that everybody thinks you are a wonderful person. Those are the seven C's that I often advise to the young investigators.

HG: The award that you received in China? I wondered what specific aspect of your work that award recognized.

DMC: I think you probably meant the Academician Award of the Academia Sinica in Taiwan. Right? Yes. That was given actually for the research of my entire career. This is an award considered by many to be the highest honor given by Taiwan for research in life science, mathematics, chemistry, physics and engineering. Also in literature as well. I feel to be honored to be inducted into Academia Sinica as an Academician in 2006. This is an organization somewhat equivalent to the National Academy of Science in the US, although it's a smaller institution. Currently, we have about 270 members, and among them eight are Nobel Laureates.

HG: I guess I'm wondering what I've forgotten to ask you. Is there anything that we haven't touched on that you would love to take this moment to make sure that it's captured for the future?

DMC: Not really. I think you covered very well. I would say this is a great time for neuroscience research. At this moment, we have many important discoveries and very important tools to conduct research. President Obama

has put forward the brain initiative project. Many disease genes and disease biomarkers have been identified and we have good models, animal models and other models, for disease to conduct research. We have excellent tools, for example the brain imaging tool, the optogenetic technique and the newly developed CLARITY, which allows the detection of neurons and neuronal networks in a three dimensional manner. Many clinical trials are underway; so this is really a golden time to conduct neuroscience research. I think the same thing can be applied to other research areas as well. I hope we will continue to get the support to conduct research to make a huge progress.

HG: Wonderful. Thank you. Thank you. Thank you. I appreciate it. I'm going end.

End of Interview