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My passion for science: a fireside chat

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In Taiwan, resources (funding and research facilities) are not too bad, but access to high-quality students and postdocs limited, and research environment could be improved as well. The research environment could be more open. Young people also need to be educated on how to do science. They need to acquire the motivation and passion for science and intellectual inquiry, in general, not just learning textbook or journal science. Walking encyclopedias do not make good scientists. It is intellectual curiosity that fosters creativity. Developing scientific judgment is also important. Scientific judgment comes from experience. The funding of research does not encourage discovery science, which is high risks and long-term. Most research projects in Taiwan are short term. There is too much emphasis on quick results, which often do not contribute to the advancement of science, not to mention the growth of economy or the social well-being of the country.

I am not here to tell you how to do science. That is simply not my style. Besides what worked for me might not work for you. I have worked in science for more than 60 years, so I can recount my experience to illustrate how I did it. I will relate how I got to where I am today.

First, for me I am just curious. It's all about intellectual curiosity. I had always wanted to understand my surroundings, about nature, even about human behavior, since I was a kid. So my interest in science is rather personal. I like to make a good living too and could have started a business on my own, but decided that it was more satisfying for me to do science. So it was for rather selfish reasons.

What is scientific research?

Scientific research is about asking questions about nature, physical, chemical and biological phenomena, and the world we live in, and digging deeply to seek the answers. Research is search, search, and search again until you are intellectually satisfied with the answer. So it takes hard work, discipline, patience, fortitude, a degree of stubbornness; in other words, mental stamina. So it is not for everyone.

To me, science is not about research grants, research publications, awards, or ego trips, although it is difficult sometimes to separate the human element from the science in the pursuit of truth. As humans, living is about survival, so money, power, and fame are important. I see the advantage of having wealth, power and fame, because they can open doors for me to do what I want to do in life, but I am not driven by them.

Since my curiosity in science was instilled in me by many teachers, I decided very early in my career to be an educator, to offer and create opportunities for young people to learn and understand more about the world I live in and to contribute to it. In other words, I was interested in developing fellow scientists. I came from very humble beginning (I was brought up in a ghetto, not just poverty and opportunities, but also a culturally disadvantaged environment, in other words an intellectual ghetto, where nobody in the surroundings that I grew up in had any education). My parents had no formal education. So they made sure that I had one, so that I can become rich and famous, and have power. But they didn't understand my romance with science.

When I moved to Caltech, I discovered that I enjoyed teaching smart undergraduates. I also found out that I could inspire bright and motivated young people to help me fulfill my intellectual interests and goals, engaging graduate students and postdocs to do science with me, to find out about nature, physical, chemical, and biological phenomena together with me. It was inspiring to me. I found out that I was not alone with my intellectual interests. I discovered that I could accomplish more and faster with more brains than just my own. During my 60 years as an academic, I benefitted greatly by working with bright young people in a stimulating and open research environment. Caltech was a wonderful place for me in this respect.

How do I do science? How did I select the research problems I ended up pursuing? A lot of it is intuition, even serendipity. There is no vision in it. I do not have the brilliance or creativity of Richard Feynman. Murray Gellman, or Linus Pauling.

Science, and then there is science!

To me, there are three different kinds of science as the business is being practiced today. First, there is what I called discovery science, or exploratory science. Exploratory science usually begins with asking a question about something nobody knows anything or much about. Like the question Christopher Columbus asked before he embarked on his journey west to discover America. He had a hunch. So with discovery science, you are stretching your imagination and probing the unknown. You are starting with a black box, without any clues about what is in the box. This doesn't mean nobody has never asked the question before. But nobody has found the answer yet. Or sometimes the nut was too hard to crack!

Different types of research in science

1. Discovery science, exploratory science

Science that has not been done before. To me, it is the most important kind of science. Research problem needs to be defined, questions need to be asked, and research strategy needs to be developed. Looking at a black box and groping in the dark. High risks and long term. In general, high intellectual content, but low productivity, at least at the beginning.

Opportunities to open up new frontiers, new research areas. Usually low competition and not too much literature to worry about. Great for research training of students and postdocs, smart and motivated ones anyway. You train the student how to think, how to ask questions, how to define a research problem, how to come up with a research strategy, and execute the work with the highest intellectual standards possible.

2. Main stream science

Popular areas actively pursued currently by the scientific community, e.g., materials chemistry, organometallic chemistry, C-H activation, asymmetric synthesis, DFT calculations, solar cells, CO_2 reduction, CH_4 oxidation and C1 chemistry in general, molecular catalysis, bioinorganic chemistry, electro-catalysis, water splitting, fuel cells, structural biology, especially X-ray crystallography, NMR spectroscopy, cryo-EM, biological imaging, neuroscience, medical research, cancer, COVID-19, protein folding and misfolding, protein design, artificial intelligence, machine learning, quantum computing etc.

The collection of topics change over time. When I started my academic career, the issues were totally different: natural product synthesis, physical organic chemistry, chemical dynamics, surface science, molecular spectroscopy of various kinds, especially NMR, ultrafast spectroscopy, molecular beam scattering, electron scattering, quantum chemistry, etc. The scientific issues were mostly defined, and solutions were within reach. No intellectual breakthroughs or paradigm shifts expected now.

Scientific breakthroughs are driven by fundamentally new ideas, hypotheses, new methods and techniques not yet discovered.

As examples- Discoveries of fullerene, carbon nanotubes, graphene; new methods and techniques, Atomic force microscopy, MALDI and ESI mass spectrometry, and high-performance computing. These advances are now part of main-stream science.

3. Mature science, improvements, further advances achieved by fine tuning

Issues largely defined. Understanding can still be fine-tuned or improved by additional experimentation and thinking. Frequently, the issues are revisited with new instrumentation and new methods. A lot of literature to follow. There is a lot of this kind of science that can still be performed, with occasional paradigm shifts and overturning of existing dogma. Scientific impact varies.

My research career

<u>Phase 1: Graduate study and postdoctoral training</u>

- Microwave and Far-infrared spectroscopy of oxetane, a four-membered ring. I learned quantum chemistry and molecular spectroscopy as a graduate student at Berkeley.
- Molecular beam NMR of $^{15}N_2$. I learned NMR at Harvard.

<u>Phase 2: Beginning of career</u>

- Theory of magnetic susceptibility and nuclear magnetic shielding.
- Structure of inorganic complexes in solution by NMR.
- Study of the base-stacking interactions of nucleic acid bases in aqueous solutions by solution NMR.
- Secondary structure of single-stranded nucleic acids in aqueous solution.

<u>Phase 3: Dynamic structure of the bilayer membrane</u>

- Fluidity of the phospholipid bilayer by NMR of orientation order and relaxation measurements: motions from sub- nanoseconds to milliseconds; size of the cooperative domain; curvature effects and bilayer asymmetry.
- Effects of cholesterol on the phase behavior and domain size.
- Passive transport of solutes, especially ions. across the bilayer membrane.
- Interactions of peptides with the bilayer membrane.
- Lipid-protein interactions.
- Lipid mediated protein-protein forces and distribution of proteins in the membrane.

<u>Phase 4: Membrane proteins</u>

- Cytochrome c oxidase (Complex IV): ligand structures of the metal cofactors; electron transfer; O_2 binding; redox-linked proton pumping; bioenergetics.
- Bacterial oxidases.
- Complex III: cytochrome bc1.
- Complex II: succinate-quinol oxidoreductase.
- HCO_3^-/Cl^- anion transporter in the red blood cell.
- Glucose transporter.

<u>Phase 5a: Protein folding</u>

- Protein folding and misfolding.
- Earlier kinetic events in protein folding.
- Development of ultrafast caging methods to study the early kinetic events in protein folding.
- Protein folding a manifestation of kinetic channeling in the folding of a hetero-polymer.
- Instability of proteins as the reason of amyloid formation in neurodegenerative

diseases.

Phase 5b: C1 chemistry

- Biological methane oxidation in pMMO.
- Development of a biomimetic methane oxidation catalyst that operates at room temperature.
- Selective oxidation of light alkanes.
- Mechanism of PQQ-dependent hydride transfer in the conversion of methanol to formaldehyde in methanol dehydrogenase.

Summary

I have had a great career and have enjoyed every moment of it. I have benefitted greatly by having inspirational teachers who offered me encouragement when I was young, and later on, many professors at UC Berkeley, Harvard, and colleagues at Caltech, who opened doors for me during my career. I was fortunate to land a teaching position at Caltech, where I had the opportunities to rub shoulders with smart undergraduates, worked with motivated and creative graduate students and postdocs, and stimulated by great colleagues.

Basically, I grew up in science by doing it. My research career consists roughly four phases, and it evolved from one phase to the next. I did not stick to any one field. When A. Zewail asked why I was leaving chemical physics or physical chemistry, I responded by saying that I was bringing what I have learned in chemical physics and physical chemistry to life science. I have tried to do mostly discovery science, because I thought this form of science provided the best opportunity for me to train motivated and creative graduate students and postdocs. The science I did has been mostly ideas driven. Also, I prefer to be in the front of the pack and not to join the bandwagon.

I was fortunate enough to have random-walked into scientific issues that later became mainstream. So I was able to participate in developing these areas of science and to get out when it is time to move on. I do not enjoy competing with others and nor am I into one-ups-man-ship. I do not like the limelight. I am more of a loner. After all, I am just an educator, or a scientist, a thinker or an intellectual at best.

My legacy to science: not my science, whatever I did accomplish or not, but the students I have trained, who have gone on to do better science than I did, and even opened up new fields. I have been an administrator: many years at Caltech as Executive Officer in chemistry, Master of Houses, and Chair of Caltech faculty, and a number of years here in Taiwan as Director of the Institute of Chemistry and YT Lee's Vice President at Academia Sinica. But in retrospect, I cannot say that I enjoyed these responsibilities. Basically, I do not like to tell people what to do, or to worry about people's dirty linen. I only did it to try to make the place better for everybody, namely, provide service as a good citizen.

I suppose I could have succeeded with a different career. My mother wanted me to be a medical doctor. I did try and dropped out. My father wanted me to be an engineer and return to China to rebuild the country out of poverty. I did get my B.S. at Berkeley as a chemical engineer. But discovered that I was more interested in ideas than applications. I could have ended up like many of my cousins as a teller in the bank, a post office clerk in the US Postal Service, a grocery checker, or a butcher. I could have ended up as a high school science teacher and enjoyed it.

When I turned 50, my dad wanted me to take over the family business. That would have been a nightmare for me. I do not like wheeling and dealer. Besides I am too honest. With all of these other career choices, I would have been bored my entire life. Now at 85, I decided that I have made the best possible career choice for myself. So I am satisfied and happy!

Should I have expected more. No! After all, someone is paying me to do what I enjoy doing most. It’s the best of all possible scenarios!

Current topics in Biophysics

- Single-molecule spectroscopy, fluorescence, light microscopy, and super-resolution imaging
- Single-molecule genomics, epigenetics
- Single-molecule microbiology
- Soft and living matter organization and dynamics
- Bio-photonics
- Nanoscale biology
- Single-cell analysis, microfluidics
- Computational biophysics: MD simulations, coarse-grained simulations, theoretical biopolymer physics
- Protein Design
- Biological self-assembly and cellular organization
- Cell signaling, immunity, nano-imaging
- Machine learning, nano-bio-optics
- Cryo-EM
- New methods and techniques

Epilogue

Being at the right place and at the right time is important in Science. So you need to keep your eyes open, or your ears open. In other words, you have to alert as to what’s going on. Good luck!