Journal of Innovative Optical Health Sciences
Vol. 7, No. 2 (2014) 1330004 (11 pages)

DOI: 10.1142/S1793545813300048

World Scientific
www.worldscientific.com

Britton Chance's lab and thereafter: From NIR spectroscopy to molecular sensing via nanotechnology

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Received 15 September 2013
Accepted 16 September 2013
Published 22 November 2013

I was fortunate to work with/for Dr Britton Chance as his postdoctoral fellow, in the Biochemistry and Biophysics Department at the University of Pennsylvania, between August 1991 and January 1994. As anyone who worked for him, I had a sufficient dosage of "Britton Chance" over the years. Initially, to me, I felt that he was someone who was above regular people and far away to reach. Then I became to know him as a person, who was simple and complicated at the same time, with a persistent pursuit for his life interests, i.e., the advancement in science related to human health. As far as it goes to science (and perhaps with sailing), he had few boundary: He communicated with any age group, any one from any country with any cultural background. Any scientists were welcomed to his lab, his own house, and even his boat. He was happy with minimal material things. He kept his friendship faithfully. From him, I came to know how much one person can actually do during a life time. I am very grateful that I got to know him during my life path. In this paper, I list some of my experiences with him scientifically and also how and what I learned from him impacted my research and personal life.

Keywords: Biosensing; molecular sensing; contrast agent; Nanoparticles; cancer detection.

1. Meeting Dr Chance and Working for Him

I am not sure exactly when I first met Dr Chance but I know it was during one of the annual conferences of the International Society on Oxygen Transport to Tissue (ISOTT). Then, in August 1988, during the ISOTT conference in Ottawa, Canada, he asked me to have a breakfast meeting with him, which made me nervous because of his internationally known reputation in science and because I hardly knew about him in person. During the meeting he offered me a postdoctoral position in his laboratory, working on the topic of near infrared (NIR) spectroscopy. I was very much surprised because he did not know me well and he could

always have many good postdoctoral candidates from all over the world. At that time, I was a PhD student in the Chemical Engineering Department at the University of California, Davis (UC Davis). My professional/academic training before I began my PhD studies was mainly in biomedical engineering in the field of mathematical modeling and computer simulation of oxygen transfer to tissue, and heat transfer during the cancer hyperthermia. This training was mainly by Dr Duane F. Bruley, who has been another life-long mentor of mine, is one of the two founders of ISOTT, and a long-time colleague of Dr Chance. For my PhD, I was involved in the affinity purification of Protein C, a natural anticoagulant in blood plasma. I particularly selected this topic before I came to UC Davis because I realized the coagulation and anticoagulation in the body was directly linked to the oxygen transport, and this protein was still not well known in the scientific community, despite its importance in the body. Although my research project for my PhD study was Protein C purification, I was still doing mathematical modeling and computer simulation of oxygen and heat transfer in human body.

Until the time of Dr Chance's offer, I never worked on optics except for using UV-Vis spectrometer without realizing it was an optical instrument. I told him that I would think about the offer seriously. He later sent me several papers related to the NIR spectroscopy. When I read the papers, although I did not understand the content fully, I found that NIR propagation in tissue is by diffusion and consumption, just like the oxygen or heat transfer in tissue, but at a rate six orders of magnitude faster. For this postdoctoral fellow opportunity, I was intimidated because I always felt I was not a very good researcher and I was not sure what was expected in the Dr Chance's laboratory, which was considered to be one of the best in the world. After seriously thinking about my future, I took his offer, thinking that I would learn what would be like working in a highly competitive research environment.

I arrived in Philadelphia in August 1991. I briefly saw Dr Eva Sevick who was the postdoctoral fellow, immediately before me, leaving for her first professorship. Although I am not absolutely sure, she might have been Dr Chance's first postdoctoral fellow who had traditional engineering training, which makes me to be the second one. She was not only a brilliant and energetic researcher, but also has excellent skills in oral and written communication. One of her papers, describing the NIR technique for biomedical application,[1] helped me enormously in understanding the theory and application of NIR. When I arrived in Philadelphia, I found that things were completely different for those in Davis California. If I could choose a color representing Philadelphia, with my mental status at that time, it would be gray. The city had a fast daily-living dynamics and also it looked much more dangerous to me, who was used to Davis life style. In the lab, learning about NIR and biooptics was one thing but trying to understand the work environment with highly competitive people was another thing. Basic and applied scientists and clinicians from the Johnson Foundation (Richards Building) to the Hospital (HOPS and CHOPS), all of them were intermingled and working independently and together at the same time; very chaotic but still moving forward. In the lab, there were always so many visiting scientists from all over the world and many seminars in the library. The research topics discussed in the library were from fundamental biochemistry and biophysics to bioengineering, clinical study, etc.

Shortly after I arrive at PENN, I asked Dr Chance whether he would want me to work on a particular research topic selected by him or I could choose a topic of my interest. His words were "Do whatever you want". At that time, I was not quite sure whether he really meant that or not but, in fact, he allowed me to work on the topic of my choice. First I had to learn about the propagation of the NIR light in the tissue. The two main biomedical applications of NIR at that time were obtaining oxygen saturation in the tissue using the measurements of the NIR intensities and phase shift; and the light propagation in the homogeneous tissue and in the tissue with heterogeneities to locate/characterize bio-heterogeneity. Many researchers in the Chance lab were involved in obtaining accurate oxygen saturation values in the tissue by measuring the NIR absorbance by the oxy- and deoxy-hemoglobin. Oxymeters are currently used in the hospitals but it is for the arterial blood oxygen saturation not for the tissue oxygenation. The tissue oxygenation is complicated to obtain because the chromophore used for computing oxygen saturation is hemoglobin and it is inside blood vessels, not in the tissue. The tissues consume oxygen, but the measuring must be done from the

chromophore in the blood, which complicates the study. Clinically important heterogeneities in the body, for me at that time, were the pulsating blood vessel and the breast cancer. Arterial pulsation rate could be easily obtained via measuring the light absorption by the pulsating artery that transports red blood cells containing hemoglobin, a strong NIR absorber, and then transferring the data to the frequency domain.[2] In terms of cancer detection by NIR, because cancer tends to develop blood vessels around it, hemoglobin, the absorber, is also accumulated around it. Therefore, the tumor becomes a localized absorber. Since a tumor (i.e., localized absorber) consumes more photons supplied by the NIR source, the light passing through the tissue with a tumor has less photons and the mean pathlength is different from the one passing through the tissue without the tumor. I soon translated the photon transport in the tissue as in the way that the oxygen transport in it: The system included the source (NIR source), and the light is transported by diffusion and consumed by the tissue, if there is a tumor the consumption rate for the tumor is assigned to be greater than the one for the tissue. I applied my previous computer simulation experiences in oxygen transfer to the photon transport, and solve the resulting photon transport equations by the B–W–K (Bruley–Williford–Kang) technique, a probabilistic numerical technique developed by Dr Bruley.[3] Since then, this technique was used for our mathematical models and computer simulation for NIR transport in tissue.[4,5]

The basic concept of analyzing the NIR data obtained from the tissue is exactly the same concept as the "Systems Identification Theory", which has been used in the identification of engineering systems' behavior for years. In the traditional system identification technique, the system to be analyzed is treated as a "black box", and the system to be analyzed by NIR spectroscopy is human (or animal) body or organs. Figure 1 shows the three NIR input source shapes which are most frequently used for the tissue characterizations, and their respective outputs.[6] In the engineering system identification, to characterize the system behavior, it is disturbed with input of a particular form and the output signal is analyzed in terms of "transfer function" in the frequency domain. In the MRI image analysis, the same principle has been used for a long time but the communities of the engineers and the imaging have been using two different languages. With the

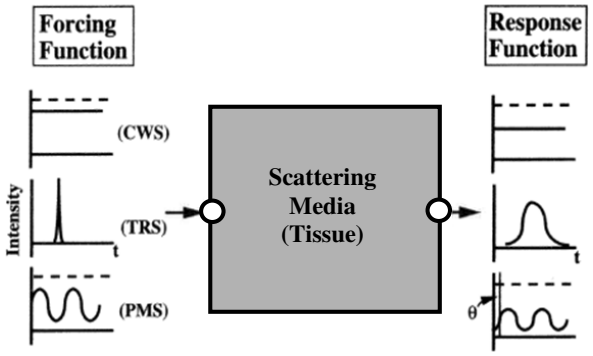


Fig. 1. Interpretation of NIR spectroscopy in terms of the systems identification theory.[7] Three different input forcing functions are frequently used in NIR spectroscopy, i.e., the step function [continuous wave spectroscopy (CWS)], pulse (TRS), and sinusoidal wave [phase modulation spectroscopy (PMS)].

help of Dr Bruley, who is an expert in systems identification theory, we analyzed the NIR time resolved spectroscopy (TRS) data in a nontraditional way. The data taken in time domain were converted into frequency domain, and then the changes in the phase delay (in optics; phase) and magnitude ratio (intensity) were analyzed. By doing so, one can obtain phase and intensity information at multiple modulation frequencies from a single TRS spectra.[7–10] Figure 2(a) is a schematic diagram of a TRS input and an output. Traditionally they were analyzed by fitting the experimental data to the mathematical model. When a single set of TRS input and output data, in terms of the transfer function, is transferred to a frequency domain one can have the intensity and phase information at as many frequencies as desired [see Figs. 2(b) and 2(c),[10] respectively], assuming the input pulse is very close to a shape of a Dirac Delta function (i.e., very sharp). The usual way of analyzing frequency information in the systems identification theory is through the system parameters of (1) the magnitude ratio (MR, intensity in NIR spectroscopy); (2) phase shift (ϕ; phase in usual NIR analysis); (3) steady state gain (K); (4) time constant (τ); and (5) system order (n). Theoretically, if the pulse input for TRS is sufficiently sharp (close to Dirac Delta function), then the MR and ϕ values at any modulation frequency may be obtained. Considering that the light at a high modulation frequency penetrates less into the tissue and *vice versa*, and the multi-frequency information is available from a single TRS measurement, this analysis technique can potentially provide the three-dimensional information

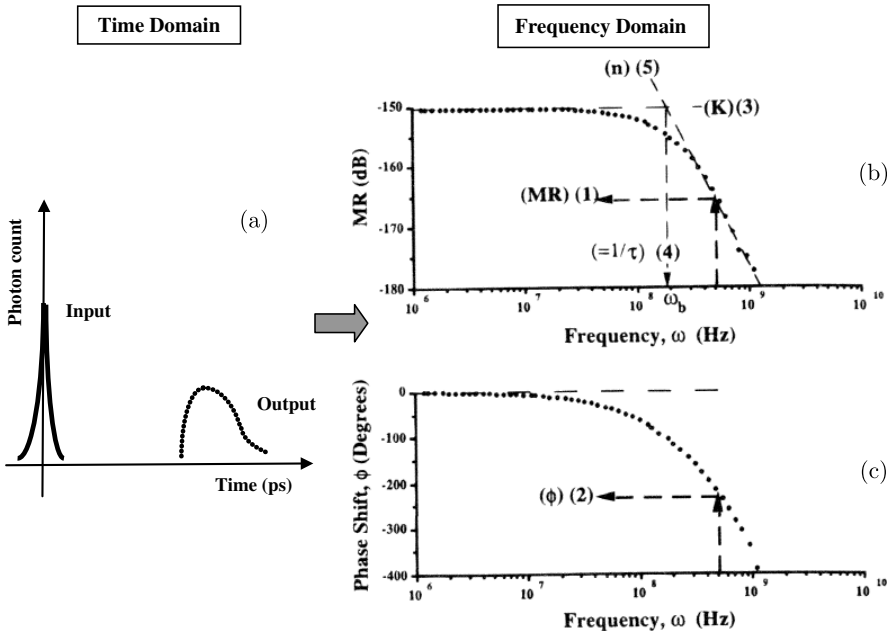
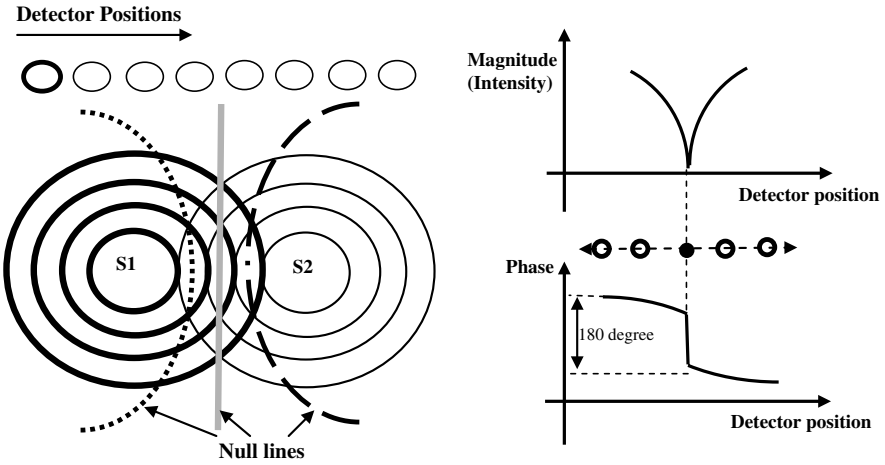


Fig. 2. Transferring time domain information of TRS input/output to frequency domain[10]: (a) Magnitude ratio (intensity) and (b) phase shift (phase). Five parameters defining signatures of a system: (1) the magnitude ratio, MR, at various frequencies; (2) phase shift, ϕ, at various frequencies (3) steady state gain, K, (4) time constant, τ and (5) system order, n.

from two-dimensional experimental data.[10] In practice, the TRS input is probably not sufficiently sharp enough to have the MR and phase values greater than 1 GHz.

Another important research topic that I was involved was the NIR phased array. One day, Dr Chance came with a completely new approach of analyzing the NIR phase modulation spectroscopy. Most of us who worked with Dr Chance knew that, during the World War II, he worked for the US government project in the Radiation Laboratory at the Massachusetts Institute of Technology to develop highly efficient radars. One of the projects was related to the phased array. For the NIR research, he decided to use the phased array concept to localize tumor in tissue, similar to the radars locating an aircraft in the air. Initially, I did not quite understand Dr Chance's intention with phased array concept and I just thought he was trying to use the Doppler effect for NIR. Soon, I understood exactly what he meant to do, which, I thought, was a brilliant idea. When there are multiple sources generating sinusoidal waves with an evenly distributed phase difference (e.g., 0°, 30°, 60°, 90°, 120°, 150° and 180°), then the wave front can cover the area of interest. If there is any inhomogeneity in the medium, which prevents smooth wave propagation, then one can detect its location by analyzing the pattern of the wave propagation. The main difference between locating flying object in the air by radar and locating a tumor by NIR in human breast tissue is that the NIR light intensity rapidly decreases as it propagates in the tissue, while the radar signal gets transferred very far and sweeps the large area of interest. Therefore, the exactly same concept of the radar phase array may not be applied to NIR very well.[11] Therefore, some modification was done in the original concept of the NIR phase array.

The new NIR phased array became as follows: Two identical NIR phase modulated waves with a 180° phase difference are placed on the surface of an organ (e.g., breast tissue) to examine, at a predetermined distance between two sources. As the NIR waves from the two sources propagate into a relatively homogeneous tissue media, there forms a plane with a zero-light intensity at equal distances from the two sources [see gray line in Fig. 3(a)] — the light intensity with 180° phase difference [in the middle plane of the two sources; Fig. 3(b)]. Dr Chance called the plane "Null Plane". In a media with a localized absorber (and also scatterer), it disturbs the smooth propagation of the waves and the position of the null plane moves to the side of the absorber [the dotted or dashed line in Fig. 3(a)], unless the absorber is placed along the middle plane.



(a) (b)

Fig. 3. Schematic diagram illustrating the NIR phased array with two sources with a phase difference 180°.[11] (a) The wave propagation in the media. In a homogeneous medium, the null plane (gray solid line) is equi-distant from the two sources. When the absorber is on the left or right side of the center line, the null plane moves to the left (dotted line) or right side (dashed line), respectively. (b) The magnitude and phase measured at the detectors on the opposite side of the source: At the null plane, there is little light intensity and 180° in the phase shift.

Assuming that a detector is placed at a position along the middle line from the two sources, when the source/detection unit moves around the area of interest, if the detector senses light, it means that the heterogeneity is located close to the unit. We did numerous computer simulations and also experiments using intra-lipid solution an black absorber, and the concept was verified.[12–15]

Another study that I performed was optical imaging of an object containing NIR fluorescence contrast agent indocyanin green (ICG), which, later, became important in my current studies of nanoparticle contrast agent development.[16]

In terms of clinical studies, I was involved in obtaining optical properties of breast tissues, with and without cancer, from the subjects visiting the Radiology Department at the University of Pennsylvania.[17] Working in the hospital with medical doctors, clinical staffs and patients was very different from working with mathematical or experimental models. Because the surgery usually starts very early in the morning we had to be at the hospital before 7:00 am. Many times we did not have any data collected because subjects did not want to participate. In addition, our measurements should be done during a short time period while the X-ray technicians checked the film or the instrument, without interfering any of their routine practice. Nevertheless, we learned a lot from the measurements. Personally, I also learned about rules and regulations involved in the human study and about getting approval from the Institutional Review Board, which helped me for my own human studies later.

When I joined Dr Chance's lab he was already 78 years old and two years later we had his 80 year birthday party. So many scientists from all over the world came to celebrate his birthday. For me, it was also interesting to meet his colleagues, and former students and postdoctoral fellows during Dr Chance's birthday party. At the party, I met Dr Francis Jobsis for the first time and it was also the last time I would see him. At the PENN Johnson Research Foundation, I was lucky to also know another great researcher Dr Mildred Cohn. She once invited me to a dance performance and I was so surprised to know that she was also a dancer when she was young. She used to give dance lessons to children to support her study, she said. She told me about her late husband and her life as a wife, mother, and researcher. In 2003, the Johnson Foundation at UPENN organized a scientific symposium celebrating the 90th birthday of both Drs. Chance and Mildred Cohn. The symposium was excellent as usual participated by about 500 people from all over the world. The phrase used for this birthday, by the organizer, was BC MC XC. The birthday party was at the Philadelphia Museum of Art, and the sign of "BC MC XC" was illuminated on a balance beam of the museum.

All these experiences at the Chance Lab have guided my future research career development in one way or another.

2. After Chance's Laboratory

2.1. *At the university of maryland baltimore county*

In January 1994, I took an assistant professor position in the Chemical and Biochemical Engineering Department at the University of Maryland Baltimore County (UMBC). At the UMBC, I worked for Dr Bruley, who was the Dean of the College of Engineering, at that time. I began to form my own research group with more independent research topics. For NIR studies, research on the breast cancer continued.[18,19] In addition, we expanded our NIR study for detecting deep vein thrombosis in the leg,[20–25] which would be the frequent problem with people who are immobile and especially the ones with anticoagulant deficiencies, such as protein C, protein S, antithrombin III, etc. In another biooptics study, I also performed a multi-spectral analysis of skin anomalies for noninvasive characterization of skin cancer types. Combining technologies of the biooptics that I learned from the Chance group and of the immunoaffinity mechanism that I learned from Protein C purification, my team developed highly sensitive, fluorophore-mediated biosensors that can quantify the Protein C level in blood plasma for diagnosing Protein C deficiency. This sensing system was highly specific and sensitive. Since the reaction occurs on the surface of the optical fiber, it can be real-time sensing. This project was later expanded to develop a portable, highly sensitive, multi- anticoagulant and multi-cardiac marker sensing system.

My research group owed a lot to the research support by Dr Chance. Since my team did not have any NIR instruments, Dr Chance allowed me to use his. My students and I frequently drove to Philadelphia to take the measurements, about which the students were always so excited. My students discussed our study results with Dr Chance, which made Dr Chance, me, and my students happy, connecting three generations of scientists. Dr Chance also gave a recommendation letter for one of my M.S. students for his medical school application. Later, with a grant from the National Science Foundation, we built our own NIR-TRS instrument. Dr Chance also sent us one of his Run-man units (an NIR continuous-wave spectroscopy) for our project of deep vein thrombosis detection in the legs, which became a joint research project with Johns Hopkins University.

Immediately after I left the PENN, the PENN established Britton Chance Distinguished Lecture in Engineering and Medicine, which I always tried to attend although I often could not. While I was at the UMBC, I invited Dr Chance for a lecture. Despite his busy schedule he kindly accepted our invitation. In addition to this, there were several times that he tried to help me, behind the scene, including writing a letter to the Chancellor of the University Maryland, which I found later accidentally.

2.2. *At the university of louisville and the research still connected to Dr Chance*

In 2000, I moved from UMBC to the University Louisville (UofL) in Louisville, Kentucky, where I belonged to the Chemical Engineering Department. At UofL, I became to have more colleagues in the medical school than at UMBC, especially at the James Graham Brown Cancer Center. I invited Dr Chance again for a lecture and the lecture was at the UofL Medical School. Many people came to his lecture and they really enjoyed his lecture. Even now, many still talk about the lecture. The Brown Cancer Center later invited Dr Chance for their annual symposium for cancer metabolism two more times, and he accepted the invitation for both.

In 2006, I organized the annual ISOTT conference in Louisville, Kentucky and Dr Chance

Fig. 4. Dr Chance giving his invited lecture during the annual International Society on Oxygen Transfer Tissue (ISOTT) in August 2006, Louisville, KY.[26]

attended the meeting. Figure 4 is a photo of Dr. Chance while he was giving an invited lecture during the conference.[27] A scariest situation occurred during a dinner function at the Frazier History Museum: Dr Chance suddenly fainted. We called emergency medical service (EMS) and they examined him thoroughly. I think he forgot to eat his meals regularly during the conference because no one reminded him to do so, and, therefore, his blood glucose level probably went down too low. One thing that I noticed about Dr Chance was that, when he was ill, he rarely complained. When he was ill he became slightly more irritated than usual and it was a sign that one had to pay attention to him. Otherwise, he would just keep working. The EMS people wanted to take him to the hospital to further check his conditions but he strongly objected to the idea. He said "I came to do science. I am not leaving". After taking some soup he became better soon and he mingled with other scientists again. Next morning, I was so relieved to see him again in the scientific sessions sitting at the first row of the room. He was fine when he left for Philadelphia.

Then, until 2010, I visited Dr Chance once a while, when I had meetings in Philadelphia with my students and, sometimes, to attend Britton Chance Lecture series. When I visited him, I would discuss with him on what I had been doing.

My research with NIR at the University of Louisville continued for detecting breast cancer. In my opinion, breast tissue is a good candidate for detecting biological inhomogeneity (in our case, breast tumor) because of its relatively low hemoglobin concentration compared to other tissues, which allows the tumor to have a better optical contrast. Nevertheless, breast tumors can be still difficult to detect by NIR light when the tumor is small and/or located deep inside the tissue. Therefore, our emphasis on NIR spectroscopy became in developing safe NIR contrast agent with good breast cancer targeting ability. The only NIR fluorophore that can be used for human is ICG and my study for application of ICG as a fluorescent contrast agent was initiated when I was at Dr Chance's lab.[16] As a fluorophore, it has a very low quantum yield (0.002 in blood) but still provides better contrast than the blood in the tumor vasculature.[27] Certain nanosized metal structures can change the fluorescence of fluorophores significantly, when they are placed near the fluorophore. The range of the fluorescence alteration can be from complete quenching to extensive enhancement. Since gold is inert and nontoxic to human, we further explore the possibility of using gold nanoparticles (GNPs) in developing optical contrast agent for molecular imaging of breast cancer. We developed a novel GNP-ICG complex in such a way that the fluorescence is emitted only at the breast cancer site that secretes a particular enzyme and at an enhanced level, which possesses both specificity and sensitivity for the cancer diagnosis.[28–33] Whenever I had opportunity to talk to him, I discussed about this project results with Dr Chance and he strongly recommended me to perform animal studies immediately.

In 2008, I started to be involved in characterizing a complete new circulation system called the primo vascular system. This system is distributed in the entire body and is to be the organ responsible for the acupuncture therapy. It stores small cells expressing stem cell biomarkers and appears to be involved in cancer cell transport. When I visited Dr Chance in 2010, which was my last meeting with him, I showed some of the images of this new system and discussed about this new system.

3. Personal Statements

I had known Dr Chance for 20 years and it seems that I came to know more about him after I left his laboratory. Everyone has his/her reasons to be here on the earth but it seems that he had many reasons to be here. Although I got to know about him only during the later years of his life, I learn about many unique aspects of this unique person.

3.1. *Dr Chance was always curious about new scientific findings, and adapted himself to new technologies*

One phrase that always made Dr Chance's eyes sparkle was "Guess What?" Any scientists were welcomed to his lab, and frequently to his house. There were always seminars immediately outside his office, i.e., at the Johnson Foundation Library. His house in Philadelphia is big and beautiful (a historical monument), and has many rooms. Poor Dr Nioka always ended up taking care of the needs of the un-expected guests' room-and-board. At the dinner table in his house, with these guests, he liked to discuss about the updated research results. If the day fell into Saturday, for the ones who were invited

and willing to go to New Jersey then they went sailing together and continue to discuss about science. He always asked so many questions, during the scientific meetings. One of my former students once told me that the conference organizer should prepare a microphone just for him. He was also a true sense of engineer, eager to realize his scientific ideas to actual tools that can be used for human health.

When I was working for him, he was still using slide rules but did the calculation faster than I could do with my calculator. But he was not afraid of using new tools if he believed the new tool was helpful for his science. Even during the short time as I was at PENN, there were series of changes in the communication mode from the phone and FAX then to the email and Skype, etc. He used all of these means if they could get him the information fast. When I saw him the last, approximately one year before he passed, he lost freedom of moving around by himself and he did not have secretary at PENN. He was revising a research proposal using "track change" in the MS Word by himself.

3.2. *Dr Chance always worked very hard, multi-tasking, with little waste of time*

I worked for Dr Chance at his late seventies and early eighties. He usually came to his office at around 7–8 am in the morning and stayed until 5–6 pm in the evening. Some of his former students/postdocs told me that, when they worked for Dr Chance, he was always in his office/laboratory by 7:00 am if not earlier. He would work for the entire day and discussed about the results with them. Early in the evening, he would go home for dinner with his family, and then come back to the lab. By then they were expected to be ready to show the results on their previous discussions on that day. When I had a chance to visit his house in one late evening, working on a joint research proposal, I saw him working at night until he fell into sleep on a sofa. Later, Dr Nioka brought over a warm blanket, and covered him with it very gently not to wake him up.

He also had an ability of reading very fast. He would vigorously write so much in the famous "Britton Chance" notebook, while he talked about science. His writing was so clean that I was always able to read what was written. While he traveled, Dr Chance would communicate with his secretary by phone or many times by FAX. One day, his secretary Dot jokingly said that "I just found that there is FAX machine in the airplane now". He always carried his tote bag with the notebook and very often his small recorder. Whenever he came back from his trips, Dr Chance brings many small audio tapes for his secretaries to type.

Dr Chance's mental sharpness and energy, at that age, was simply extraordinary. He remembered people's name so well. Sometimes when I discussed with him about my study results, I saw him falling into sleep right in front of me, as anyone at his age might do, but with his eyes still open. I would make fun of him by saying "Hello", with waving my hands. He would then wake up and say, "I was just thinking", and we continued the discussion. In many conferences, people often talk about him falling into sleep during presentations and waking up to ask very sharp questions.

Dr Chance did many other things, in addition to science, very well throughout his life. He appeared to have an amazing ability of compartmentalizing each item. He was always positive and once he set his mind for a task, he never stopped in the middle. We all know that he won an Olympic gold medal in sailing and has a relationship with the sport in his entire life. He loved his country and he was a part of the important task force of the "MIT project" during the World War II. After the 9/11, he considered applying NIR technology for homeland security. A few times when I visited Dr Chance after the work, I saw him playing piano and, sometimes, with Dr Nioka playing violin. In Dr Chance's laboratory, many different things were going on at the same time and there were always some type of chaos: There were international researchers going in and out of the lab; there were seminars every day; instruments were moving to so many different places; grant proposals were always due and so many different sections of proposals were sent from one to the other researchers, etc. Nevertheless, somehow, amazingly, things always got into the right track at the end.

3.3. *Dr Chance welcomed anyone to his life and he was a wonderful mentor for many scientists, even for children*

Because of Dr Chance's accomplishment and fame, when people met him for the first time, many were often intimidated by his presence. Nevertheless, he

communicated with everyone who contacted him: he responded to any letters or emails that he received, even during his busiest time. He would write or dictate his letter back to any letter he received. When the email became the mode of daily communication, one of his secretaries would print them out and gave them to him. He would then write his response on the printed email and gave it back to the secretary to reply. There was no racial, gender, national, and age boundary to Dr Chance. Dr Mildred Cohn once told me that Dr Chance was one of only a few male researchers who would support female researchers from the early time. Whenever I visited his lab with my own students, he would always talk to them about their research and, very often, he wanted them to present their research results.

I am sure that it is almost impossible to count so many scientists who were mentored by him. In addition to these professional scientists, every summer, Dr Chance had a research program for under-privileged high school students in the inner-city of Philadelphia. One day Dr Chance called me to ask the name of the Director of the National Science Foundation. At that time, he wanted to request funds for this summer research program for these high school students. These junior researchers/students did research with Dr Chance in his laboratory, just as any other mature scientists, and he had weekly meeting with these students. Some of them, as high school students, actually had their names on scientific papers as coauthors with Dr Chance.

3.4. *Dr Chance had interesting routine activities*

Every morning without exception, Dr Chance communicated with people via his HAM radio. I am sure that whoever happened to stay in his house overnight would have heard this HAM radio sound in the morning. Every Saturday, after his morning work in the laboratory, he went to his house in New Jersey shore to sail and he would bring his work along there. When he had guests they were assumed to go along with him. The scientific discussions continued in the car and in the New Jersey house. Annually, there was only one long vacation for him, at least during the time that I worked with him. He went to Florida for sailing with his family and scientists during Christmas Break. I have visited his house in the New Jersey shore but I never sailed with him, which I regret now. I was told that he always wrote about his experience on the trip.

3.5. *In Chance's laboratory, there were people consistently supporting him to be great*

When I was working in his laboratory, there were Chilton who did not mind sharing his fore head with scientists measuring NIR signal from his brain, and sweet Henry who drove Dr Chance everywhere he needed to go.

We often say that, behind all great men, there are always great women. For Dr Chance, during the time that I associated with him, there were at least three ladies who worked almost as a part of him. Mary Leonard is the artist who produced the figures and tables for Dr Chance's publications and presentations. Dorothy Coleman is the one who would perform the miracles of converting crazy grant proposal sections to presentable ones, and of delivering the package to the funding agencies before (sometimes, only seconds before) the deadlines. Dr Shoko Nioka, who was literally the shadow of Dr Chance, her love for Dr Chance was very quiet, without too many words, especially when he needed most intimate care. I thank them for their cares of Dr Chance so that we could be with him longer.

3.6. *Dr Chance has been and will be my life-long mentor*

As a person who was raised in an Oriental country, I was never able to call Dr Chance as Brit or BC — I always called him Dr Chance. Ever since I knew him, I always respect his humble life style. Material things did not seem to excite him much and he would get by with minimum. He would wear suits only for special occasion. He kept a clip-on necktie in his office closet just in case he had to appear in formal functions. Everyone in the scientific field knows about his old bike with a special horn. He went everywhere in the Philadelphia city by this bike.

Dr Chance was always supportive on my research, giving full freedom while I was working for him. He never said no to my invitation for giving lectures where I worked. He helped me behind the scene. When my parents visited me in Philadelphia he (and also Shoko) was very kind to them although my parents did not speak English and he did not

speak Korean. This visit became particularly important for me, which I did not know at that time, because it was the time that I spent with my father before he passed away by cancer only a few years later. When my father was terminally ill Dr Chance suggested me talk to Dr Cohn because her husband died by cancer and he thought she could give me some valuable advices. When I visited him in 2010, the last time that I saw him, during the annual Britton Chance's lecture series, he told me that I should do animal studies with my nanoparticles immediately, which was probably the last advice from him.

I am grateful that I had a ***Chance*** to work for/with Dr Chance. Sometimes, I smile or even laugh by myself, with my memories of him. For the Dr Chance's 100th birthday Symposium, I think that he was irritated for not being able to attend and to ask questions, but I am sure that he was very proud to see many of his seedlings he raised.

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