PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES

Britton Chance 1913–2010

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DEDICATION

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A week after our meeting, we received the very sad news that Britton Chance had passed away on 16th November 2010, in Philadelphia, aged 97. Britton was an extraordinary scientist who made an enormous impact in so many areas of biochemistry and biophysics. He was a leading figure in biomedical optics over many decades and organized the Royal Society Scientific Discussion Meeting on 'Near infrared spectroscopy and imaging of living systems' in 1996. We include here some reflections from members of our community who worked with him and knew him well.

1. David Boas' recollections

I remember well first meeting with B.C. near the end of my first year as a Physics graduate student. I was interested in probing turbid media with diffuse light with Arjun Yodh. Arjun, who was studying colloidal systems with diffuse light, suggested that I speak with B.C., who was studying tissue with diffuse light, to see if I could work to bridge between physics and biomedicine with my PhD research. B.C. was easy-going, ready to give anyone a chance, and I left our first meeting looking forward to starting my research with him and Arjun in the summer. Over the years, I always admired this willingness to give everyone a chance. I equally admired, though, that he fully expected you to rise to the occasion and had little tolerance for those who did not. I saw numerous research assistants appear and then disappear. More importantly, I saw many appear and then excel as they rose to and met his high expectations, and then go on to become highly successful in setting up their own research endeavours around the world.

B.C. created opportunities for everyone around him. When I was in school, I always appreciated that he treated students the same as full professors. While you could observe an occasional feather-ruffled full professor, B.C.'s approach clearly had bi-directional merit. Junior colleagues benefited tremendously from meeting with the numerous leaders who would frequently visit the laboratory, while the visiting senior colleagues were able to engage the highly energetic junior colleagues, oftentimes leading to collaborations lasting long after the initial meeting. This sort of leadership style strengthens a community, and I strive to mimic it myself. From my perspective, this generous leadership quality, as much as B.C.'s tremendous scientific achievements, helped to create the vibrant and highly engaging and collaborative biomedical optics community that we know today.

One contribution of 20 to a Theo Murphy Meeting Issue 'Illuminating the future of biomedical optics'.

Figure 1. Preparing for departure for a 3 h tour of Boston Harbour after the 2002 Molecular Imaging Conference. (Online version in colour.)

Interacting with him taught me the power of a broad perspective. He was multi-disciplinary decades before the importance of this was understood by most. Who knew that disparate fields such as ham radio technology (his work since childhood) and cellular energy metabolism (starting in the 1930s) could be connected? B.C. connected these with great success with his early work in magnetic resonance spectroscopy (1980s). Following his lead, I strive to be engaged in different fields, so that I may cross-fertilize between them to help accelerate scientific progress. His example here also demonstrates the importance of pursuing with fervour any innovative idea born from this cross-fertilization, even if others initially fail to see the importance.

In the acknowledgements of my PhD dissertation I wrote [1]:

> BC's uncanny ability to sort through numerous ideas, seemingly similar and orthogonal, and pursue a long term goal has kept me pointed in the right direction at times when forces were pulling me every which way. A treasure chest of new research projects is a curse without the ability to stay focused on a well-defined track. I am also grateful to Brit for the many opportunities that he directed my way despite my sometimes hesitant approach. His faith in my abilities has gone a long way towards my intellectual growth.

My years with B.C. were an exciting time with numerous exciting ideas pulling us in many directions. I have been fortunate to remain in such an environment since then. Without his repeated guidance on identifying and chasing the best question, I would have gotten lost years ago. It took me years to catch on, but his insistence of extracting information from every experiment, despite my hesitance

at the time, is key to rapidly progressing one's scientific effort. I would probably still been worrying about phantom validation of the diffusion equation if not for B.C.'s guidance here.

Finally, B.C. exemplified the importance of balancing hard work with hard play by always making the time to go sailing. While I always felt that such a balance was important, outside pressure seemed to suggest that one needed to work all waking hours in order to succeed. I believed that this was inefficient and that breaks were needed for the brain to subconsciously work through and help solve the problems of one's work. B.C.'s example helped give me confidence that this was the right path. Reflecting back over the years, I can recall numerous problems solved and novel new insights that occurred while walking through the woods or along the beach, or even while sailing. I have no doubt that B.C.'s love of and devotion to sailing strengthened his scientific accomplishments throughout his career (figure 1).

2. Chris Cooper's recollections

I first met Brit at Brock University in Canada in 1987. My PhD supervisor, Peter Nicholls, a long time associate, had invited him to give a seminar. I was somewhat in awe, given all the stories that were associated with his life and science. As he was in his seventies by then, I assumed I would meet a somewhat slowed down version of the great man. Not a bit of it. He had to rush off after the seminar as he had 'beam time' booked on the Synchrotron at Cornell. He was working on the structure of mitochondrial cytochrome *c* oxidase, the subject of my PhD thesis. For biomedical optics was, of course, only a part of his work; another love was the mitochondrion and oxidative phosphorylation. Throughout the 1960s, 1970s and 1980s a succession of the future world leaders in bioenergetics passed through the Johnson Foundation in Philadelphia. It was rare for me to meet an academic in Europe who had not spent at least a year there.

I only managed to get to the Foundation once in 1997. Arriving jet-lagged off a plane at six in the morning for what I assumed was a pleasant chat and tour of the laboratory, I was led into a room. Brit sat at a table surrounded by graph paper and chart recorder traces. Without even a coffee being offered, I spent 2 h being quizzed on the current academic argument between the two of us; surely I did not really believe near-infrared spectroscopy could measure mitochondrial cytochrome oxidase in the body? After a tough 2 h grilling—interrupted only by the occasional student delivering data and Brit plotting extra points on the graph paper—I learnt two things. First, Brit is great at probing your data and suggesting key controls; second, never, ever, ever, enter into a meeting with Brit unprepared.

We can see how much I learned from this encounter by studying my last meeting with Brit. This was at a conference he loved to attend—the International Society on Oxygen Transport to Tissue (ISOTT)—at Uppsala, Sweden in 2007. I gave a talk on cytochrome oxidase (what else). Brit was—as usual—seated in the front row. But time had started to take its toll. He was fast asleep throughout my presentation; my luck was in. I finished my talk and the Chair asked for questions. Suddenly, Brit shot up (or at least that is what it felt like). He said 'Cecil—either he had forgotten my name or was trying to unnerve me, I could never tell which—Cecil, where did you get that number you used in your model'? However, I was

Figure 2. The cytochrome oxidase team. (Online version in colour.)

prepared this time; quick as a flash I chimed that if he was referring to the rate constant for oxygen binding to cytochrome oxidase, of course I had used the $4 \times 10^7\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$ value that Chance used in his seminal 1955 *Journal of Biological Chemistry* paper [2]. There was a pause … then in a reasonably polite, quiet drawl Brit said 'No—I meant the numbers you used for the diffusion limit for chemical reactions'. I paused, nonplussed, frustrated; Brit added, 'Chris, don't you remember the work of Smoluchowksi in 1917 [3]?'. Putting aside visions of the 4-year-old Brit, devouring scientific papers while the first World War raged around him, I retired suitably chastened to my hotel room.

Figure 2 shows Brit sandwiched between the formidable couple of Helen Davies (née Smith) and Lucile Conrad (pictured on the right) at the 1987 American Society of Biological Chemistry Meeting in Philadelphia. Helen was the first woman ever to receive the American Medical Student Association's National Excellence in Teaching Award; Lucile was the first woman to become a full professor at Dartmouth Medical School. This picture illustrates all that you need to know about cytochrome *c* oxidase. This enzyme binds the protein cytochrome *c* and oxidises it with oxygen. The cytochrome *c* kinetics were characterized by Smith and Conrad; the oxygen kinetics by Chance. So, growing up scientifically in the 1980s, I had not only to learn about Brit's famous five states of mitochondrial oxygen consumption, but also the classic 'Smith-Conrad' paper explaining the cytochrome *c* kinetics. It is to my eternal misogynistic shame that I imagined Smith-Conrad to be an ageing English kineticist with a suitably posh double-barrelled surname ….

Even though I only knew him in his later days, Brit was an inspiration to me, and of course to many others. He was as comfortable in hard-core biochemistry as he was in non-invasive magnetic resonance spectroscopy or biomedical optics. I spoke to Peter Nicholls just after he had returned from attending Brit's memorial

meeting in Philadelphia in June, 2011. A cytochrome biochemist, who had known Brit for over 50 years, Peter was surprised to see that most people at the meeting knew Brit mainly for his exploits in biomedical optics. My research covers both these fields (though of course at a far inferior level to Brit's). I would never have had the courage to follow such a dual career without the shining light of Brit's example that it is possible to care about the life of the molecule and the organism at the same time. Not for him the multidisciplinary collaboration of a biochemist with a physicist/engineer. Instead he was a true interdisciplinary master of both trades, able to make insights at the interface that would have been impossible for lesser mortals. It was always an honour to be humbled by him.

3. David Delpy's recollections

I first met Brit in the late 1970s when I started to regularly attend the annual meetings of the ISOTT. This was a society that had been formed in 1974/1975 and of which Brit was one of the founding members. I was a young researcher working on blood oxygen and carbon dioxide sensors using electrochemical, mass spectrometry and gas chromatography techniques. The research community attending ISOTT was small, but they were all highly knowledgeable in their research area, so presenting papers and posters there was always guaranteed to provoke a lively (and challenging) discussion. There were a few attendees whose knowledge was almost encyclopaedic, one of whom was Brit, the other main one being Dietrich Lubbers (a German physiologist whose significant contributions in the field are often disgracefully overlooked). Brit and Dietrich would always sit in the front row of the lecture theatre (on opposite sides) and were guaranteed to ask a highly penetrating question of every speaker, no matter what the subject of the session! As an aside, in later years, Brit would often sit in meetings giving every impression of being asleep (perhaps he was), but at the sound of the applause at the end of a talk would leap up and still ask a penetrating question!

Brit always brought along quite a few students to the ISOTT meetings and at lunch break, when the rest of us were relaxing and gossiping, they would grab their plates then sit in a group around Brit discussing and summarizing what had been presented in the previous sessions. Like most of us, Brit was an extreme workaholic, and this was really brought home to me when he visited my group shortly after we had first described our 'time of flight' measurement of optical pathlength in the rat head. After a day with him in the laboratory, my colleague Susan Wray (now Professor of Physiology at Liverpool), invited Brit and the rest of the group for a relaxing dinner at her home. We had an excellent evening, but I am not sure you would call it relaxing with Brit continuing to grill everyone and scribbling notes in his laboratory book, which sat on his knee all evening!

Brit was a true polymath—he had two PhDs (one in Physical Chemistry from University of Pennsylvania, the other in Biology and Physiology from Cambridge). He was an outstanding experimentalist with a real feel for electronics and instrumentation, as a result of which he invented numerous techniques and instrumental methods that are now used universally. (I do however feel that he much preferred analogue electronics to digital techniques which I think he felt

stopped you understanding the underlying principles of the measurement). He was also a scientist who enjoyed commercializing his ideas and was the founder of several companies through which he marketed his ideas.

Although this quite rightly is a eulogy to an exceptional scientist, I must close by saying that he was not totally infallible. When he first met me he must have misheard my name, and for the next couple of years as session chair or questioner at conferences would always address me as Don Delpy!

4. Marco Ferrari and Valentina Quaresima's recollections

Marco Ferrari was acquainted with B.C. from the middle of the seventies, since he met him during several Biochemistry meetings held in Italy.

Although B.C. has been one of the main founders of *in vivo* visible reflectance spectroscopy, B.C. and Shoko Nioka only started to work on *in vivo* near-infrared spectroscopy (NIRS) in 1987. Indeed, NIRS was discovered in 1977 by Frans Jobsis (Duke University) who, by the way, learned the techniques of optical monitoring of intact tissues as a postdoctoral fellow in B.C.'s laboratory at the University of Pennsylvania in 1962–1964 (figure 3).

From 1985 we were in touch regularly, either attending almost every year the meetings organized by ISOTT, the International Society for Optical Engineering (SPIE), the Organization for Human Brain Mapping and the American College of Sports Medicine, or promoting together with other colleagues the field of quantitative brain/muscle oximetry and functional NIRS (starting in 1993).

Among the different common experienced initiatives, we wish to mention the SPIE Meeting, 'Photon Propagation in Tissues III', we organized pleasingly all together in San Remo (Italy, September 1997) and the meeting held in Rome, Italy, the following month (9 October 1997) organized by the University of Rome 'Tor Vergata' to give B.C. the Honorary degree in 'Medicine and Surgery'. For the latter occasion, all the leaders of Biochemistry in Italy and the other pioneers of medical NIRS David Delpy (UK), Arno Villringer (Germany), Enrico Gratton (USA) and Martin Wolf (Switzerland) came to Rome to honour him (figure 4).

B.C. came to Italy again in August 2004 to attend the 32nd Meeting of ISOTT that was held in Bari (figure 5).

Although Marco Ferrari and Valentina Quaresima (who joined the laboratory in 1991) were never trained in B.C.'s laboratory, they had the great honour to be estimated and considered by B.C. as his close friends. B.C. was always interested in their work and he was available to give helpful suggestions. In 1997, Valentina Quaresima had the great privilege to write with B.C. and other outstanding scientists (Hamaoka and McCully: B.C.'s previous fellows), a milestone review article published in the *Journal of Biomedical Optics*. In the article, they reviewed the methodological issues of NIRS and NIR imaging for monitoring muscle oxygenation and haemodynamics in healthy and diseased humans and highlighted the significant applications of NIRS and NIR imaging in exercise physiology and clinical medicine.

B.C. will be greatly missed, both as a special person or as a great scientist from our medical NIRS community.

Figure 3. B.C. and Frans Jobsis (Duke University) during the meeting 'Optical imaging of brain function and metabolism' that was held in Garmisch-Partenkirchen (Germany), 21–22 October 1991. (Online version in colour.)

5. Arjun Yodh's recollections

Sometimes you get lucky in life; it was my good fortune to join the Physics faculty at Penn in the late 1980s, and then, shortly thereafter, to cross paths with Britton Chance. Following the discovery of the Diffusing-wave Spectroscopy technique in the condensed matter physics community, I began experimenting with fluctuating, multiply-scattered light to measure the Brownian dynamics of particles in dense (turbid) colloidal suspensions. I had never heard of Britton Chance, but one of my colleagues suggested he might be interested in our work. Following this suggestion, I walked to the Johnson Foundation and introduced myself to Britt. Britt was indeed very interested in our work, and I found Britt's work fascinating. I wanted to apply our experimental tools to tissues, and Britt, as always, was very encouraging. We met on several occasions over the next year

Figure 4. Arno Villringer, Marco Ferrari, Britton Chance and David Delpy during dinner at a restaurant in Rome to celebrate the honorary degree in 'Medicine and Surgery' (Rome, Italy; 9 October 1997). (Online version in colour.)

Figure 5. Mamoru Tamura (Japan), Valentina Quaresima (Italy) and B.C. at the 32nd ISOTT meeting that was held in Bari, Italy (21–26 August 2004). (Online version in colour.)

and agreed that it would be fun to do experiments together. Finally, we decided that if we were to work together, then we must pick up some PhD students that we could jointly supervise.

Thus, the true catalysts for my long-term collaboration with Britt were two talented PhD students from the Physics Department (David Boas and Maureen

O'Leary), who were very open-minded about 'what constitutes physics'. Together, the four of us managed to carry out many elegant physics-oriented diffuse optics experiments in a fish tank, some of which introduced or demonstrated important ideas, at a very early stage, about what could be done with diffuse light. Britt was excited by this activity, and we were talking almost every day about the experiments and about what to try next.

During this time, I came to know Britt much better, and I found out about a few of his 'other' accomplishments. Britt, of course, never let his past accomplishments interfere with our collaboration. He was a very secure man, who treated me as an equal—always. I was quickly introduced to essentially everyone else in the field. All of these people came to visit Britt, and Britt was always excited to bring new colleagues together and to share notes on the latest developments. I have many lasting friendships as a result of this community building that Britt facilitated (more on this point later).

On the technical side, Britt's skill in radio frequency-electronics was remarkable. I remember bringing a new commercial lock-in amplifier into the laboratory, so that David and Maureen could carry out experiments more easily; David and Maureen were very glad to have the commercial lock-in amplifier, but, in retrospect, I suspect that Britt must have been gritting his teeth (he never said anything). Britt would have preferred us to 'build' the lock-in amplifier from scratch. At the time I believed such thinking to be a little crazy, but now we build instruments in my laboratory with IQ-chips, etc., following Britt's lead. Britt was 'inside' the electronics boxes; he really understood how things worked. Britt was also stubborn about his opto-electronics ideas. One of his favourite ideas was the so-called phased-array device. Britt liked it, in part, because of the intuition he had built up with radar. The idea was interesting to me, but I never thought it was the best approach in the digital age, and I did not always believe the sensitivity he was claiming. We debated about it a great deal. But Britt was a very persistent man, and he kept working with the concept through his final years—and, who knows, maybe it will turn out to be the best approach for hand-held devices.

After 5 years of focusing mainly on fish tank experiments and the physics side of things, I felt confident that I understood these problems well enough to start applying them to the human body. Britt was glad to have me aboard. Of course, Britt had not waited to get a 'perfect' understanding (another useful sensibility I have since acquired from Britt). He was already shooting light beams through the body in the Hospital at the University of Pennsylvania (HUP), among other places. Britt had enough intuition about the physics and the physiological problems to start interesting projects. Over approximately the last 15 years, we had fun working together on a variety of projects which focused on the human body. In our continuing discussions, Britt patiently taught me about metabolism, haemodynamics and tissue physiology, and Britt also generously introduced me to many scientists and clinicians at HUP who were anxious to explore the utility of the new technology. One important contribution combined two of Britt's favourite technologies, MRI and Diffuse Optical, to probe breast cancer; our talented PhD student, Vasilis Ntziacrhistos, made this idea work in humans for the first time—and helped initiate multi-modal approaches with diffuse optics. Many of Britt's other visions are also finding fruit these days, including hand-held and tomographic approaches to breast cancer characterization, monitoring brain

function and trauma, and probing muscle energetics. As a result of these efforts, I also learned a lot from Britt about the pursuit of parallel projects and goals—this approach permits one to do more, and, perhaps more importantly, ideas from one sub-field invariably influence progress in a second sub-field in unanticipated ways.

Returning to the topic of Britt's contributions as a community builder, permit me to make a few closing remarks. I have worked in many different fields, and they each have a unique sociology. Britt was a force defining the sociology of our field of Biomedical Optics, and we are better as a result of his efforts. Britt organized tirelessly, collaborated tirelessly and he promoted the field without fatigue. He made special efforts to encourage and promote young people in the field, as well as those colleagues around him at Penn. He had crazy ideas (or not so crazy) to pool intellectual property and know-how, so that scientists in our community might get a bigger piece of the pie. Whether you agree with the philosophy or not, he did it for the community. For me, I am grateful for his community building, because it has enabled me to build long-lasting friendships with collaborators and with other scientists working in Biomedical Optics. I think this 'sociology' input might be Britt's most important contribution to Biomedical Optics, and I hope we can continue it!

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