What Britton Chance means to me

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My first encounter with Britton Chance was not with the man, but with his voice. It was the summer of 1964, I had just arrived in the U.S. to work as a postdoctoral fellow with Efraim Racker in New York City, and Ron Estabrook had invited me to the Johnson Foundation to give a lunch seminar on our recent discovery of mitochondrial DNA.

Shortly before my seminar, I hastily swallowed the obligatory *Johnson Foundation Speakers Menu* consisting of a cup of tepid Coca Cola and 18 potato chips and tried to pay my respects to Brit, but was told that he was busy doing a measurement. As I waited for him outside his laboratory, a wooden shutter in the wall of his darkened instrument room suddenly slid open and a flurry of recording paper covered with red tracings came flying through, landing both on a desk in front and on the floor. As the young woman guarding the desk patiently collected the papers from both locations, I heard a male voice with an elegant WASP accent say "That's all for now. Have fun with this, my dear".

This first encounter with Brit was in many ways typical of my later ones. As my own research was focused on how mitochondria are made, and not on how they work, I never collaborated with Brit, was never part of his laboratory, and never published a paper with him. Yet I saw him often, because my postdoctoral mentor Efraim Racker was one of his closest and most valued friends. The two visited each other regularly, but as their ways of thinking and of doing science were very different, a casual bystander overhearing their discussions would have concluded that they could not stand each other.

I still remember the spring day of 1965 when Brit visited our run-down and cockroach-infested New York City laboratory and Racker proudly told him that his postdoc Yasuo Kagawa had just isolated a mitochondrial protein complex that bound purified F_1 and made it oligomycin-sensitive. "How splendid, Ef" smiled Brit "but is this protein complex really from mitochondria - or from one of your cockroaches?" When Brit then gave his seminar in which he extolled the virtues of his rapid stopped-flow technique, Racker interrupted him in midsentence: "Now I know why you get wrong results so much faster than anybody else". But such banter was only their way of hiding their genuine and warm friendship.

What can I, who was never part of Brit's inner circle, say in his memory? Perhaps I can try to articulate what he meant to me who saw him only from the distance. Perhaps my different vantage point may help to triangulate the character of this complex man and to give his memory additional perspective and depth.

But let me first start with some facts. As so many of you have pointed out today, Brit was a towering figure in what we now see as the heroic age of bioenergetics. Most of the heroes of that age were born in the short time span between 1913 and 1920 and all of them have not only witnessed, but spearheaded the rise of biochemistry to an independent science.

Brit and Ef Racker, the two oldest of them, were both born in 1913, but apart from that they could not have been more different. Racker came from a poor Polish background, had no scientific training to speak of, and loved risqué jokes, rumpled suits, painting and music. Brit, on the other hand, was born into a well-to-do Pennsylvanian family and had a first-rate scientific education: a doctorate in chemistry and engineering from the University of Pennsylvania, a doctorate in biology from Cambridge University, and two years as a Guggenheim Fellow with Hugo Theorell at Stockholm University.

While sharing Ef's passion for science, Brit was much more at home in the worlds of elegant manners, sports and sartorial splendor than in those of Egon Schiele or Gustav Mahler. His outstanding skill and intuition in designing and applying complex electronic devices soon caught the attention of scientists at the Radiation Laboratory at MIT who hired the young whiz kid from Philadelphia and soon made him head of a large team working on radar and other microwave-empowered devices. Others his age would have cracked under the weight of such a demanding task, yet Brit still found enough time for sailing to win a Gold Medal for the U.S. in the 1952 summer Olympics.

And today's symposium has borne impressive testimony to his many other scientific contributions: his revolutionary stopped-flow machine capable of measuring very fast reactions; his wondrous spectrophotometers detecting minute optical changes in opaque biological samples; and his ingenious use of nuclear magnetic resonance or infrared absorption for probing metabolic events in living tissues.

Brit, more than anybody else, has given us biochemists much better eyes with which showed us what had long been hidden from our view. They showed Brit that the much-debated enzyme-substrate complex of Michaelis and Menten was not only a theoretical *fata morgana*, but a reality. And they also showed him – and his postdoc Ron Williams – that respiring mitochondria release the energy of electron transfer in three discrete steps, that these three steps are reversible, and that they produces reactive oxygen species as a corrosive byproduct.

Perhaps his most intriguing discovery was that respiring isolated mitochondria attract calcium ions from the suspending medium and that these ions act as stoichiometric uncouplers. Had he followed up this observation, he might have solved the riddle of oxidative phosphorylation a decade before Peter Mitchell.

To borrow a phrase from Ernesto Carafoli, the Gods had handed Brit the winning ticket in a magnificent lottery, but Brit neglected to cash it in. There are probably two reasons for this neglect. The first reason is that up to the middle fifties of the last century, biochemistry was still very much part of chemistry and biochemists, like chemists, thought of chemical reactions in scalar terms rather than in terms of distinct spaces. This limited scalar view also prevented Erwin Chargaff to grasp the immense implications of his historic discovery that DNA always contains equimolar amounts of A and T and of G and C. This stoichiometric riddle could only be solved by a new generation of biochemists who intuitively thought in in three dimensions. Brit interpreted the depletion of calcium ions as binding to, rather than as movement into, the mitochondria.

The second reason for Brit's neglect may have been his way of doing research. He was the man of the quick and elegant electronic measurement – and studying these calcium movements in more detail would have forced him to spend many tedious years in the ugly trenches of wet biochemistry. Brit just was not cut out for this type of work, even though his willingness to work endless hours was second to none.

This aristocratic disdain for the petty detail also showed in his manuscripts which were the nightmare of journal editors. The countless errors, omissions and internal contradictions in his manuscripts would have amply justified rejection, but their scientific weight and Brit's scientific standing made this next to impossible. As a result, editors had to spend hours listing all the revisions that would make the manuscript just barely publishable. Later, when I myself worked as editor for the JBC, I recalled the paper tracings sailing out of Brit's lab through the wooden shutter and wondered whether Brit's technicians simply mailed them straight on to our Editorial Office.

In a similar vein, Brit's lectures were a barrage of complex slides – and when at the end someone was imprudent enough to ask a question, Brit quickly conjured up another dozen slides from his weighty briefcase which he always carried with him. But these idiosyncrasies could not dim the aura of this great scientist. And if one measures a scientist's legacy by the number of successful former students and collaborators, Brit probably outshines most other biochemists of his time.

Brit's long life has been remarkable by any measure, but simply recounting it cannot do it justice. There is more to Brit than his biography. To me, he was the ultimate researcher. In order to explain myself, let me now reflect on the essence of a researcher's craft.

Nobody has outlined this essence more clearly than the bacteriologist George Packer Berry when he addressed an incoming class of Harvard medical students several decades ago. His words went something like this: "This great university will do its best to teach you the latest in scientific knowledge – but about half of what we shall teach you is probably wrong. Unfortunately I cannot tell you which half". This confession shocked and even scandalized the parents in the audience who were paying through the nose to have their children trained at Harvard, yet it was merely an apt reminder that there is so much more to science than the collecting ordering and teaching of facts.

The eyes of science are not focused on knowledge, but on ignorance. A researcher tries to convert ignorance into knowledge and is usually much more interested in the act of conversion than in the product. Most true researchers consider the knowledge they create as a byproduct, the ordering and administration of which they readily leave to others. To them, a textbook of biochemistry is not "biochemistry"; it is the history of biochemistry – a summary of what they already know or at least should know. True biochemistry is to them a revealing discussion in the laboratory, a seminar on a new discovery or a helpful hint by a colleague. The home of a researcher is not the safe haven of proven knowledge, but its outermost fringe where one faces the darkness of ignorance.

Scientific knowledge is not a commodity we can neatly wrap up, label, and store forever in numbered bins. It is a zoo of strange wild animals that tear at their confines, break through the walls of their cages and interbreed into strange new creatures. Jean Paul Sarte has once said "It is not we who make war; war makes us". The same is true of our scientific knowledge. It changes continuously and thereby changes us. We may be able to control it briefly, but in the long run it always gains the upper hand. It obeys its own laws which we can neither understand nor control. The famous quote: "Nothing is as irresistible as an idea whose time has come" is wrongly attributed to Victor Hugo, but it is nevertheless true.

We researchers are not too much disturbed by the ephemeral nature of scientific knowledge. Our relationship with knowledge has always been ambivalent: we want to create it, but once we have created it, we distrust it and try to prove it wrong. Owning knowledge is less important to us than the conviction that we can always create it anew by observation and critical reasoning. Existing knowledge reflects the past and is thus never sufficient to deal with an ever-changing world.

To master the present, need the youthful force of scientific discovery. We need people who see what everybody sees, but think what nobody has thought before. We need courageous minds which are not afraid to set sail for far-away waters if these hold the promise of discovery. The American writer John A. Shedd has said it as follows: "A ship in harbor is safe. But that is not what ships are made for".

In the real world, most scientists deal with the administration and teaching of scientific knowledge. Only a small minority, the active researchers, transform ignorance into knowledge. And among these active researchers there is an even smaller minority of exceptionally creative minds who achieve the ultimate goal of science: To create new ignorance. To discover something of which we did not know that we did not know it.

When Gregor Mendel discovered the units of inheritance, Sigmund Freud the subconscious, or Max Planck the energy quantum, they opened up vast new continents of ignorance which invited exploration and forever changed our view of the world.

Knowledge is important, but we tend to overrate it - in our schools, at our universities, and even in our laboratories. It is on this point where Brit has left me his most important legacy. He showed me that science is all about pushing forward into the unknown. That's why I shall always remember him as the ultimate researcher. He had no ambition to rival Al Lehninger or Lars Ernster in their encyclopedic knowledge of biochemistry, Bill Slater in his mastery of running journals and scientific societies, Ef Racker in his writing on the broader implications of science, or his all too numerous colleagues who reveled in belittling the work of others.

Some saw this intellectual aloofness as a reflection of his aristocratic roots, but it was really the impatience and single-mindedness of a researcher in pursuit of discovery. Like a full-blooded hunter, Brit only thought of the prey he was tracking and not of the venison he might bring home. His cavalier attitude towards writing papers or giving lectures was just another facet of this hunter's instinct, but this single-minded impatience may also have cost him the Nobel Prize.

When Manfred Eigen won the prize in 1967 for his temperature jump method that could dissect chemical reactions even more finely than Brit's stopped flow approach, he publicly regretted not being able to share the honor with Britton Chance.

All this now seems of little importance, because to us and to future generations. Brit will always be Nobel caliber. In our universe, he will always shine as a star of the first magnitude, a symbol of intellectual power and the passion of discovery. Let us now stand in his honor.