

Special Issue Guest Editors

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Celebrating Britton Chance

Britton Chance is amazing; he has won prizes ranging from an Olympic Gold Medal to the National Medal of Science. In preparation for writing this piece we have been sitting at my desk pouring over the incredible work Brit has done during his scientific career. We have known Brit for over a decade, and have collaborated with him on many exciting projects related to optical imaging and spectroscopy in tissues. While pondering how best to proceed, a remark from a letter catches our attention. The comment notes that while many distinguished scientists have enjoyed "retirement" at similar stages in their careers, Brit has expanded his efforts to develop spectroscopy as a noninvasive analytical tool for clinical diagnosis. The interesting point for us, however, was that the comment was written in 1983 and refers to in-vivo NMR spectroscopy! Brit was 70 at the time.

Britton Chance is one of the giants of biochemistry and biophysics. His vast contributions have opened new fields, and have changed the way we think about old problems. His research draws from many disciplines, particularly electronics, clinical medicine, biology and physics. Throughout his career Brit has repeatedly consumed groundbreaking ideas and techniques from the whole of science, and then redirected effort toward a critical problem that benefits from his integrating approach—all in a manner reminiscent of the feedback devices he knows and loves! Finally, his ability and desire to promote scientific colleagues, and important science, technology, and application has arguably been as vital as his explicit scientific contributions. In what follows we will highlight some of Brit's achievements. This is not a definitive account; such an account would result in a very interesting document, but would require more scholarly attention to detail. Instead we have drawn together bits of the story from conversations and a few extended interviews.

Britton Chance was born in Wilkes-Barre, Pennsylvania, in 1913, and shortly thereafter moved to Philadelphia, where he resides to this day. His interests in practical chemical engineering problems were stimulated by his father, who developed a chemical detector for carbon monoxide that replaced "canaries" in coal mines, and by his uncle, who worked with early fluidized beds using mixtures of sand and water to change the density of the resultant fluid so that slate floated to the liquid surface.

Brit's family loved boating, and he spent much of his youth in the bays of New Jersey. He learned about instruments that were critical for navigation, such as radio (wireless) commu-

nication and ship steering. His first significant contributions to science and technology were in ship steering, while he was still a teenager. Ships weighing as much as 20,000 tons were difficult to steer, and rapid feedback control was desirable in order to keep these very heavy objects moving on course. Brit used light reflected from a mirror coupled to a compass needle to achieve this goal; when the ship got off course, both the compass needle and the reflected light would move. Photodetectors were used to register the motion of the light beams, and a feedback signal was generated and used to re-direct the ship steering mechanisms. The invention was patented, and Brit helped test it on a three-month trip from England to Australia in 1938 aboard the *New Zealand Star*, a refrigerator ship carrying tin to Australia and meat to England. Brit spent many summers during his youth sailing, fishing and experimenting with William Beebe and friends down in Antilles and the Canal Zone. Beebe was developing a bathosphere for extended underwater observations at the time, and one legend suggests that Brit beat out a young Ernest Hemingway in a race to catch a great blue marlin. The mounted marlin is still on the wall in the living room of Brit's Philadelphia home. This love of sea and intense competitive spirit for boating would later prove useful in the 1952 Olympics, where he won an Olympic gold medal in sailing.

The first phase of Brit's scientific career in biochemistry and biophysics was spread between the University of Pennsylvania and Cambridge University. For certification he obtained two PhDs, one in physical chemistry from the University of Pennsylvania in 1940, and the other in biology/physiology from Cambridge University in 1943. His work focused on enzyme-substrate compounds, particularly their reaction kinetics. Glen Millikan was a critical collaborator at this stage. Millikan and Chance developed a stop-flow apparatus in which the ingredients of a chemical reaction are injected into a tube and are made to flow together down the tube; the reaction is then monitored at various points downstream corresponding to different time points in the reaction kinetics. The flow can be stopped, allowing the reaction to proceed, and then restarted in order to resolve the faster kinetics. Brit pushed this scheme to new levels of sensitivity and sophistication with the aid of J. P. Harvey. He developed a microflow version of the apparatus that was critical for studies of enzymes and their intermediates, because only small amounts of material were available for investigation. Downstream he used beams of light to interrogate the changing compositions

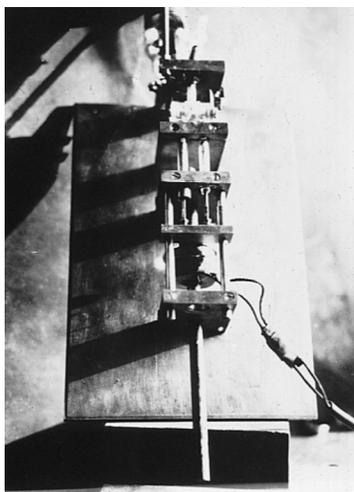


Fig. 1 Original stop flow apparatus for studies of enzyme-substrate kinetics.

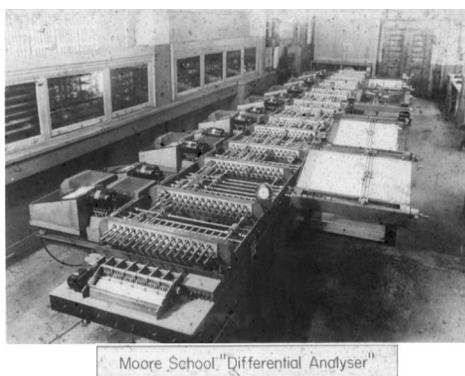


Fig. 2 Mechanical computer used with J. G. Brainerd in 1939 to solve the nonlinear differential equations representing enzyme-substrate kinetics at the Moore School of Engineering at the University of Pennsylvania.

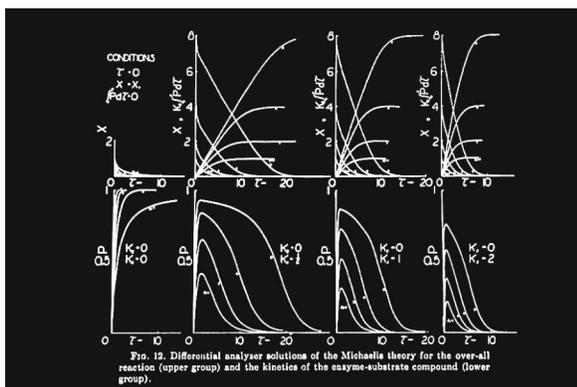


Fig. 3 Solutions of the enzyme-substrate kinetics from the differential analysis in 1939.

of the flowing sample; he identified molecules by their absorption spectra.

The highpoint of this work was the elucidation of the peroxidase enzyme-substrate reactions. At this time there were still many open questions about the way enzymes worked. There were theories, such as that of Michaelis-Menten (1910), hypothesizing the existence and action of enzyme and substrate compounds. However, no experimental observations had been made. Brit and his colleagues carried out the first detailed investigation of enzyme kinetics, and conclusively demonstrated that the enzyme-substrate complex formed rapidly, was short-lived, and that the enzyme came off intact at the end of the reaction. Furthermore, in 1938 with G. Brainerd, he successfully compared the kinetics observations with mechanical analog computer solutions mimicking the same nonlinear differential equations. These mechanical devices were fascinating—in order to change a reaction rate constant, Brit had to physically change the size of a gear in the device. The level of quantification afforded by the instruments and by the analog computer was new to the field. These experiments helped put the Michaelis-Menten theory on a firm foundation.

Between 1941 and 1945 Brit joined the war effort, focusing on radar as did many young physicists and engineers of the time. He went to the MIT Radiation Laboratory, and in a short time his considerable scientific and organizational talents became apparent. He was named group leader of the Precision Circuits Section of the Receiver Components group in 1943, and was elected to the Steering Committee chaired by Lee Dubridge and I. I. Rabi. By 1945 he was supervising 300 people as Associate Director of Lee Haworth's Division of the Radiation Lab. Among his achievements were the development of precision circuits to measure the submicrosecond time delays between the emission of a radar pulse and the detection of its echo. This device provided critical ranging information for anti-aircraft gun-pointing systems. He pushed hard to incorporate analog computers along with ranging equipment in bombers; thus a simple calculation that took into account the plane speed, wind speed, and target range was used to bomb strategic sites. In a similar vein he invented a ground position indicator (GPI) bombing system. In this scheme the target latitude and longitude coordinates were input into an analog computer, and the current position of the bomber was continuously updated in the computer by radar tracking. These two pieces of information were then combined to direct the pilot to the bomb release site. This idea was eventually commercialized. Brit remembers this period fondly. He speaks of many inspirational colleagues, lots of new ideas for devices, circuits, computer applications, and more. He also wrote substantially for three of the 27 integrated volumes on radar technology that documented the state of the art in electromagnetics at the time (i.e., Volumes 19, 20, and 21 of the Radiation Lab Series).

After the war, Brit resumed work on the enzyme-substrate problem in Stockholm. Using the stop-flow apparatus, he and Hugo Theorell identified and tracked a coenzyme for the first time. They found a coenzyme, nicotinamide adenine dinucleotide (NAD), that transiently coupled to an enzyme, alcohol dehydrogenase, facilitating the oxidation of alcohol. The intermediate complex was revealed by a change in light absorption at 320 nm. The enzyme-substrate reaction did not proceed without the binding of the coenzyme. The process is now identified as the Theorell-Chance (T-C) mechanism.

During the same period in the early 1950s Brit was stimulated by his colleague Bill Slater, working at the Molteno In-

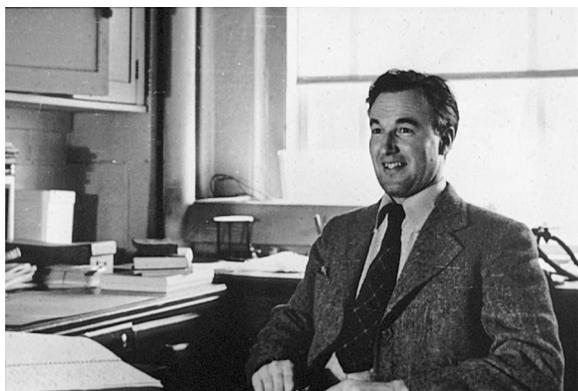


Fig. 4 Brit just after taking the helm of the Johnson Foundation from D. W. Bronk at the University of Pennsylvania in 1949.

stitute in Cambridge, to shift his attention from classical chemistry toward biochemistry in the functioning organism. Brit carried out arguably the finest work of his career at this time: elucidation of the control of oxidative phosphorylation in mitochondria. In living organisms molecular fuels are continuously burned to create the carrier of free energy which is critical for cellular metabolism, adenosine triphosphate (ATP). In aerobic organisms oxygen plays the ultimate role in driving these processes, but its electron-transfer actions are facilitated by special carriers, for example the cytochromes and reduced-nicotinamide adenine dinucleotide (NADH). Before Brit's experiments, the mitochondria were known to play a crucial role in cell metabolism, to produce ATP, and to consume oxygen and glucose products. In addition, a class of porphyrin molecules called cytochromes had been identified by visual spectroscopy of many cells and tissues. Still, big open questions remained about how mitochondria functioned: (1) What were the spectra of the critical chemical species in functioning mitochondria? (2) What were the critical ingredients in oxida-



Fig. 5 Brit puts his head in the first one-tesla magnet designed for brain magnetic resonance spectroscopy. Helman's mayonnaise was the "best fit" to Brit's brain.

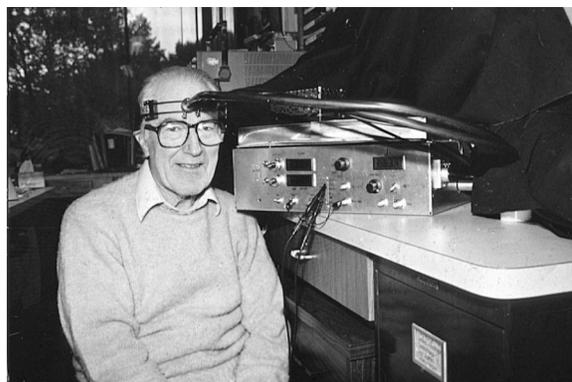


Fig. 6 Brit tests an early heterodyne frequency domain oximeter for brain studies with diffusing near-infrared light.

tive phosphorylation? (3) What specifically did these ingredients do? (4) What was the sequence of electron transfer events and what were the absolute speeds of reaction? From a practical standpoint the investigation of intact mitochondria posed many difficulties. The mitochondria scattered light substantially, they were difficult to isolate, and once isolated, they were unstable so it was unclear how to preserve their activity.

Working with Henry Lardy and later Ron Williams, Brit systematically solved these technical problems. They learned to grind cells, to separate mitochondria by centrifugation, to re-suspend mitochondria, and finally they found a chemical cocktail that preserved their metabolic activity in-vitro. The famous dual-beam spectrometer was the key to watching the mitochondria function in ATP synthesis. The device rapidly toggled between two beams of light with differing wavelengths. Typically the wavelength of one beam was chosen to coincide with the peak absorption of a chromophore such as cytochrome- a_3 ; the other wavelength was spectrally shifted by a small amount in order to provide a background measurement near the baseline of the absorption feature with similar scattering contributions. Several such pairs of light beams were employed to probe the absorption spectra of other cytochromes and of NADH. This elegant scheme, plus some sophisticated light source stabilization, enabled Brit to correct for the substantial baseline shifts brought about by heterogeneities intrinsic to flowing streams of mitochondria in different oxygen environments.

In the experiments, mitochondria, oxygen and ADP were mixed together at the front end of the stop-flow apparatus. Downstream spectra revealed the binding of oxygen by cytochrome- a_3 , oxygen reduction, and the sequential transfer of four electrons leading to the production of ATP from ADP. For example, an electron transfer event was signaled by the near-simultaneous disappearance of cytochrome- c spectra and the appearance of cytochrome- b spectra. The conversion of NADH to NAD was also observed; thus the oxidative phosphorylation process took the NADH discharged by the Krebs cycle, oxidized it, and then supplied NAD back to the Krebs cycle. In total the experiments provided a movie of oxidative phosphorylation within intact, physiological mitochondria, and revealed the role of ADP in respiratory control. The first experiments were carried out in isolated mitochondria. Later they were validated by studies in tumor cells, yeasts and in related photosynthetic systems. For good measure, Brit carried out temperature-dependent experiments in order to identify the mechanisms of electron transfer in the process. Together

with Don Devault (and with some intellectual encouragement from Willard Libby) he showed that the primary electron transfer events in photosynthetic bacteria were in essence electron tunneling processes, and thus did not involve molecular motions.

The success of optical spectroscopy for probing intact organelles stimulated Brit to push the optical method toward living tissue. To this end he initiated studies of kidney, brain and muscle tissues. Using freeze-trapped and *in-vivo* tissues he was the first to exploit the currently popular fluorescence signal from mitochondrial NADH/NAD for these studies. The large hemoglobin absorption in living tissues, however, limited the optical measurements to fluorescence, and, more significantly, to the tissue surfaces. In order to get below the tissue surface, Brit would have to develop and apply qualitatively new non-invasive spectroscopies.

His first solution to the deep tissue problem was magnetic resonance spectroscopy (MRS). Although magnetic resonance imaging (MRI) had been developed by the mid-1970s, at the time it was a slow technique, mainly used to map out the distribution of hydrogen (protons). Magnetic resonance spectroscopy, a more established technique for the spectroscopy of bulk materials, could be utilized to detect phosphorous. Phosphorous was important in all sorts of metabolic processes, and could in principle be detected via different chemical shifts in ADP, ATP, phosphoric acid, inorganic phosphate (Pi) and phosphocreatine (PCr).

Brit started experiments in small animals with George Radda and verified that PCr and Pi were the molecules to focus on in living tissues. Reservoirs of PCr are critical for survival during periods of hypoxia or intense energetic response. Under normal metabolic conditions the mitochondria are constantly converting ADP to ATP. Sometimes, however, we need more ATP than the mitochondria can supply; for example, if one is chased by a tiger, then one may need an extra boost of energy in the short term to survive. PCr can also convert ADP to ATP, and reservoirs of PCr are critical for survival because they provide an additional short-term pathway for ATP production. They thus become essential for sustaining metabolism during periods of hypoxia or stress (e.g., strong exercise). Brit, George Radda, Peter Styles and Ian Silver demonstrated the first whole organ MRS in the late 1970s, detecting PCr in the excised brain of a hedgehog (a hibernator) near 0°C. At this temperature all metabolic processes were slowed, but ATP utilization was still greater than the ATP production of tissue mitochondria. Thus Brit and Radda were able to observe the PCr signals diminishing as the reservoir was used up. This experiment signaled the start of *in-vivo* functional MRS and stimulated both scientists to obtain cryogenic magnets of

sufficient field homogeneity to measure human muscle energetics. Shortly thereafter in the early 1980s, Brit, Jack Leigh, Scott Eleff and George MacDonald first demonstrated MRS in human subjects and George Radda showed how MRS could be used to study diseased muscles (1981).

The rapid progress of *in-vivo* MRS foreshadowed current developments in optical spectroscopy and imaging of deep tissues, the subject of this special issue of the *Journal of Biomedical Optics*. Once again, Brit has been a central figure in the development of a new field. He and collaborators made a critical discovery that spurred the biomedical use of diffuse light. In this experiment temporally short, near-infrared (NIR) light pulses were injected into the brain (the light diffused through the skull), and the changes in the temporal shapes of the pulses were measured upon exit. The changes in shape quantitatively revealed the blood oxygen dynamics of the animal and, soon thereafter, the human brain in 1988. Since this experiment, the field of photon migration and optical imaging and spectroscopy has grown dramatically. Research on breast, brain, and muscle using diffuse light is an intense worldwide activity. Brit has kept his finger on the pulse of the field throughout this time period. He has worked tirelessly to advance our understanding of biology, instrumentation, and medicine by asking tough questions, making countless suggestions, and bringing together basic scientists, engineers and clinicians in dozens of scientific meetings. These multidisciplinary forums typically span the mathematics of the inverse problem, rf electronics, electro-optics, light transport in highly scattering media, acousto-optics, numerical methods, computational methods, breast cancer diagnostics, pediatrics, brain cognitive function, muscle dynamics, stroke, and more.

This special issue is a testament to Brit's powerful influence on the inception and growth of the field of Biomedical Optics. Since his first U.S. patent awarded at age 17, Brit has employed a rare combination of brilliance, drive and good fortune to become one of the most prolific scientists of the 20th century. As we enter the new millennium, we hope the remarkable story of Brit's life and career inspires your creative efforts to advance our field through the next century. "Lauds and laurels" to you Brit! We hope you enjoy the "2000 B.C." special issue of the JBO.

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