Bernard Katz
1911–2003

Stuart Cull-Candy and Donald Jenkinson

With the death of Bernard Katz on April 20th, we have lost one of the most distinguished biophysicists of our time. BK, as he was known affectionately to colleagues and friends the world over, laid the foundations for much of our current knowledge of synaptic transmission. His name is synonymous with the discovery of the quantal nature of neurotransmitter release. He will also be remembered for establishing the key role of calcium in the release process, and for the idea that acetylcholine 'noise' reflects the opening and closing of single channels ('elementary events') at the endplate. BK's work was characterized by clarity of thought and by exceptional insight into biophysical processes. His beautifully written and illuminating papers will long remain a pleasure to read.

Bernard Katz was born in Leipzig, Germany, to a Russian-Jewish family. He qualified in medicine at the University of Leipzig before leaving Germany as a refugee in February 1935 under very difficult circumstances. Arriving in the Biophysics Unit of the Physiology Department at University College London, he felt, as he once put it, "a bit like David Copperfield, bedraggled and penniless". He liked to joke that AV Hill, one of the most distinguished physiologists of his day (and a 1922 Nobel laureate), had invited him to join the lab "as an experiment". Indeed, he always considered that the turning point in his life and career was being taken on as a research student by 'AV', whose judgment, integrity and effectiveness were to be a lasting influence. By March 1938, Katz had received his Ph.D. at UCL, rapidly followed by a Beit Fellowship, at that time the preeminent junior fellowship award in biomedical sciences.

A year later, shortly before the outbreak of war in Europe, BK was invited to join Jack Eccles' lab in Sydney. Here he had the good fortune to team up with the young Stephen Kuffler, recently arrived from Vienna. For the next two years, Eccles, Katz and Kuffler worked together on transmission at the neuromuscular junction, producing landmark papers and forming friendships that were to last a lifetime. At that time, an argument still raged as to whether the nerve impulse 'jumped the gap' at the nerve-muscle junction, or whether synaptic transmission was mediated by the release of a chemical messenger (acetylcholine, ACh) as proposed by Henry Dale and his colleagues. Although Dale's ideas were gaining acceptance, Eccles continued for some time to argue strenuously in favor of electrical transmission. BK liked to tell of an incident while helping Eccles to mow his lawn. To his great embarrassment, BK cut through the power cable to the electrically driven mower, narrowly escaping serious injury. To avoid further catastrophes, Eccles exchanged the mower for a petrol-driven equivalent. BK would say (with a twinkle) that this was, in fact, the exact moment he converted Eccles from 'electrical' to 'chemical' transmission.

After war service, working on radar in the Royal Australian Air Force, BK returned with his Australian bride Marguerite (Rita) Penley to UCL as a Henry Head Fellow, to assist AV Hill with setting up the newly formed Biophysics Department. An electrophysiological laboratory was soon in operation, initially based on wartime surplus electronic apparatus that BK had reconstructed and recalibrated. He was also able to work at the Marine Biological Labs at Plymouth, where he began a seminal collaboration with Alan Hodgkin and Andrew Huxley on the ionic currents underlying the action potential in the squid giant axon.

After Hill's retirement, Katz became the Head of the Biophysics Department. In his hands it became one of the shining pinnacles of British biomedical science, attracting talented postdoctoral workers from around the world. Much of Katz's most important work there was carried out with a succession of exceptional collaborators—first Paul Fatt, then José del Castillo, Stephen Thesleff, and finally, for 25 years, Ricardo Miledi. BK was always at pains to make clear that these studies were the result of an equal partnership with friends and collaborators.

In the spring of 1950, Fatt and Katz made the accidental but ground-breaking discovery that the endplate region of skeletal muscle was the site of spontaneous electrical activity caused by the discharge of multimolecular packets of acetylcholine from the nerve terminal. Katz's elegant experiments with Fatt, and later with del Castillo, demonstrated that these so-called 'miniature endplate potentials' represented the basic coin of chemical synaptic transmission. BK always maintained that the reason he and his colleagues were able to work undisturbed on this exciting phenomenon for some six years was that most people thought they were studying an artifact! The recognition that transmitter release was quantal coincided with the discovery by electron microscopists of presynaptic vesicles. Katz and del Castillo were quick to appreciate the significance of these related findings and to put forward the 'vesicle hypothesis' (**Fig. 1**) as the underlying physical mechanism for quantal release.

They then turned their attention to the second step in the transmission process, the postsynaptic mechanism by which acetylcholine activates its receptors. In 1957 del Castillo and Katz proposed that receptor activation was not synonymous with receptor occupation, as had been tacitly assumed. Instead, they proposed a two-step model in which the first step was the binding of a ligand to its receptor and the second step, with separate kinetics, involved isomerization of the bound receptor between inactive and active states.

The 'del Castillo & Katz model' of receptor activation has required only minor modifications to make it applicable to current work (the binding of two, rather than one, acetylcholine molecules must be considered), and it remains the starting point for most discussions of receptor mechanisms. This work took forward a question first pursued in a quantitative way by A.V. Hill, some 50 years earlier (in 1909), when he applied the law of mass action to the effect of nicotine on isolated skeletal muscle. The resulting Hill–Langmuir equation had shaped many of the early ideas on how receptors function. Likewise, the del Castillo & Katz model, and the following

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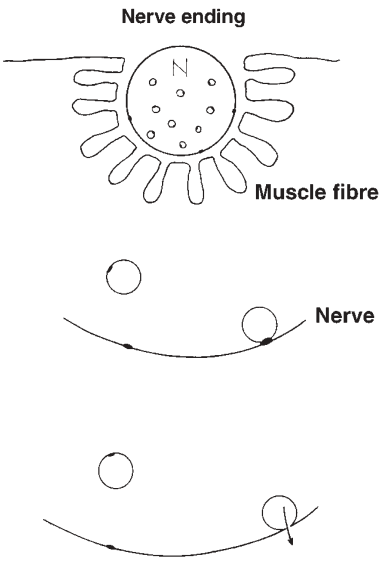

Figure 1 The classic diagrammatic representation of the 'vesicle hypothesis' proposing the secretion of transmitter by exocytosis of synaptic vesicles (bottom panel) as the mechanism underlying synaptic transmission. Presented by J. del Castillo and B. Katz at a symposium at Gif-sur-Yvette in 1955 (CNRS Int. Coll. **67** p 245; 1957, Paris).

study in which Katz and Stephen Thesleff proposed a model for receptor desensitization, have continued to present an intellectual challenge, as well as a valuable tool, for those trying to unravel fundamental receptor mechanisms.

During the 1960s, Katz, with Ricardo Miledi, returned to the issue of transmitter release, undertaking a series of exceptionally elegant studies using a focal calcium pipette to demonstrate that in the absence of extracellular calcium, a nerve impulse still enters the nerve terminal but fails to trigger the release of transmitter. This finding was followed up by experiments on the squid giant synapse, a preparation that allowed simultaneous recording from pre- and postsynaptic terminals. This work not only provided some of the earliest definitive evidence for the idea that calcium entry into the terminal was required for transmitter release, but also allowed the input–output relation of a single synapse to be examined.

Further pioneering work followed in the early 1970s, when Katz and Miledi published a series of papers on 'ACh noise'. They realised that the minute stochastic fluctuations in the membrane potential, triggered by the steady application of acetylcholine, arose from moment-to-moment variations in the number of open channels. By analyzing the spectral density of this noise, they were able to deduce basic properties of the ion channels opened by acetylcholine and its analogues. Such was the originality of these studies that the two initial *Nature* papers contained (between them) only four references to other papers, of which one was to Rice's work on the mathematical analysis of random noise, published in the Bell Systems Technical Journal. These and the subsequent full publications were an intellectual and experimental tour de force, helping to prepare the ground for the remarkable advances made possible soon after by the patch-clamp recording methods of Neher and Sakmann, which permitted single channels to be directly resolved and their detailed behavior examined.

In addition to all this, Katz managed to find time to write several books. In 1966 the classical textbook *Nerve, Muscle and Synapse* appeared. Lucid and engrossing, it inspired generations of students, including many who later entered the field. However, the book nearly failed to see the light of day. In that pre-photocopier/PC era, BK carried the manuscript to and from the lab during the writing. On the day he completed the manuscript, he left a briefcase containing the only copy on a London underground train. When he realized what had happened, he avowed he would not be rewriting it. Fortunately, the briefcase travelled on to the terminus, and hasty phone calls succeeded in retrieving it. He also wrote *Electric Excitation of Nerve* (1939), and the classic *The Release of Neural Transmitter Substances* (1969)—still widely quoted.

Bernard Katz was awarded the Royal Society's prestigious Copley Medal in 1967, and was knighted in 1969. In 1970 he was a co-recipient of the Nobel Prize. He also served the Royal Society both as Vice President and as Biological Secretary.

BK took enormous pleasure from the scientific meeting that celebrated his work and was timed to mark his 80th birthday. This meeting was attended by over a hundred of the colleagues and students from around the world who had the good fortune to work in the Biophysics Department. The immense delight that BK gained from the scientific contributions of his colleagues and ex-students was evident both in conversation and in his various review lectures. His own great achievements and influence on the subject continue to inspire and stimulate much current work on synaptic transmission. BK wished no more than that others should enjoy the same pleasure he gained from research.