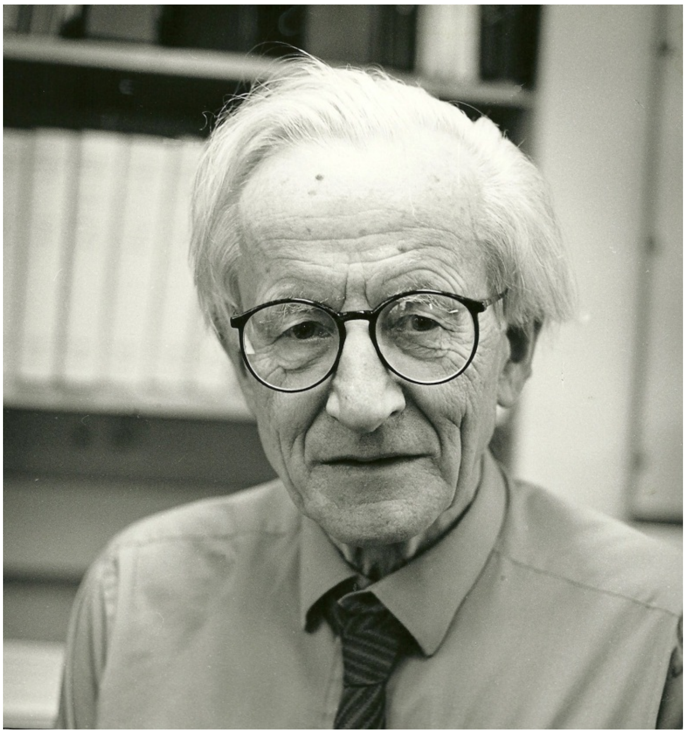
Rolf Niedergerke (1921–2011)

Member 1959, Honorary Member 1987



Rolf Niedergerke (by Martin Rosenberg)

Rolf Niedergerke was born on 30 April 1921 at Mülheim an der Ruhr, in the main industrial region of Germany. He studied medicine throughout the War, mainly at Freiburg University before finally receiving his MD at the Charles University, Prague in 1945. After the war, Rolf was briefly held by Russian troops before escaping and returning to a hospital post and local clinic work in his home city. He started his scientific studies in 1947 at the Physiological Institute, Göttingen, developing an interest in the electrical activity of nerve fibres (under Prof Hermann Rein). His first step was to set up an electrophysiological rig. Little equipment was available in post-war Germany, so he constructed much of the kit himself, gaining useful knowledge of stimulators and amplifiers and how to repair them. He succeeded in measuring diphasic action potentials and the speed of conduction in whole sciatic frog nerves (under the influence of CO_2). He was rather isolated in a department mainly working on the control of the circulation in mammals, so he was glad to be invited by Alexander von Muralt to work in the Theodor Kocher Institute in Bern, closely connected with the Physiological Institute of the University. There, Robert Stämpfli taught him to dissect single myelinated fibres. Working with Stämpfli and Eduard Coraboeuf (from Paris), and partly on his own, he measured the effect of CO_2, pH and Ca^{2+} on the threshold of isolated nodes of Ranvier and alterations of the rheobase in de- and hyperpolarized fibres. In four publications (in German) in *Pflügers Archiv*, Rolf showed himself to be a careful and methodical scientist, determined to present his results in a quantitative form, even when a complete solution had not been found.

Late in the evenings, the last people in the Institute would hear Rolf playing the flute. In his youth he had played both flute and violin in chamber music groups: music might well have become his profession had the War not intervened. Music remained a life-long passion.

Around 1951, AF Huxley had changed his interest from nerve to muscle and constructed an interference microscope to reinvestigate the striation pattern of living skeletal fibres. He sought a qualified co-worker, able to dissect single fibres and to operate a complex set-up. Robert Stämpfli, who had successfully worked with AF on single nerve fibres, recommended Rolf to him as the ideal person. Moreover, Rolf was also familiar with the work of the early German microscopists on skeletal muscle striation patterns. In 1954, Huxley and Niedergerke showed that the anisotropic ('A') bands that contain the myosin filaments do not change length during active shortening, or during passive stretch. They concluded that this observation "*... makes very attractive the hypothesis that during contraction the actin filaments are drawn into the A-bands, between the rodlets of myosin. ... If a relative force between actin and myosin is generated at each of a series of points in the region of overlap in such sarcomeres, then tension per filament should be proportional to the number in this zone of overlap*". This is a clear statement of the sliding filament mechanism, the modern paradigm of muscle contraction. The biophysicists Hugh Huxley and Jean Hanson, using different methods involving isolated myofibrils, phase-contrast- and electron-microscopy, arrived independently at the same conclusion. The two groups published their results in consecutive notes in the same issue of *Nature* (22nd May 1954). The '*birth of the sliding filament concept*' (Maruyama, 1996) was a revolution in muscle research and ultimately for the study of cellular motility overall. *Nature* celebrated the 50th anniversary (in 2004) with a short note and a photographic layout featuring the four scientists. AF and Rolf's detailed work was not fully reported until several years after their *Nature* paper (Huxley & Niedergerke, 1958).

In the shadow of this seminal work, a further study by Rolf deserves highlighting. In a *Proceedings* report to The Society (1955), he describes experiments where he applied Ca^{2+} via an intracellular micropipette in single skeletal fibres observed under Huxley's interference microscope. A brief electrophoretic injection of Ca^{2+} provoked localised shortening in the immediate vicinity of the electrode tip. Rolf suggested that Ca ions activate a link of the contractile cycle – perhaps specifically since neither K nor Mg was effective. These interesting findings, prior to the discovery of the function of the sarcoplasmic reticulum (SR), were not reported in detail – partly because of limited access to the vital interference microscope – and became neglected. However, this study indicates Rolf's new field of interest: the activation of force in muscle and the role of Ca^{2+}. He worked almost exclusively on this topic to the end of his scientific career.

Rolf moved from Cambridge to London in 1955, joining the Biophysics Department at University College. Seizing a suggestion by Bernard Katz, he changed his interest from skeletal to cardiac muscle and started to work with small strips dissected from frog ventricle. Preparations were fastened between a fixed hook and the extended anode pin of an RCA force transducer valve. Suitable strips down to 0.4 mm diameter are difficult to dissect. However, Rolf learned how to keep them functioning well for hours, to switch solutions quickly without artefacts, to measure monophasic action potentials and isometric force. With this technique, Rolf made two pioneering studies (1956*a*,*b*) of the relationship between membrane potential (E_m), beat-rate, Ca and contraction, including the use of high-K^+ induced depolarisation to control E_m.

In the autumn of 1956, one of us (H-ChL) joined Rolf to address the role of Ca in the activation of tension. Following up on prior work by Wilbrandt & Koller (1948), H-ChL and Rolf found that Ca and Na affect contractility antagonistically with twitch and contracture tension a function of the solution's $[Ca]/[Na]^2$ quotient. They suggested (1958) that Ca and Na ions attach to a membrane site that, even in combination with either Ca or Na, bears net electric charge. When Ca-bound, this complex – assumed to move within the membrane during the action potential – might promote contraction. Rolf (with EJ Harris, 1957) then revealed that this mechanism generates transmembrane ion fluxes. By using ^{45}Ca tracer, they showed net Ca uptake by cells exposed to media of increased $[Ca]/[Na]^2$. These findings and the algebraic formalism developed to describe them form keystones of subsequent work on the Ca^{2+}–Na^+ exchange mechanism (CaNaX).

As the senior author, Rolf was invited to several cardiac symposia, but he invariably declined. This characteristic reticence to push such a major new finding was regretted, in particular by those keen to promote his career and his work. (Otto Hutter has described this aspect of Rolf's personality as the "*principle-led disapproval of any form of self-promotion".* H-Ch always remained '*Herr Lüttgau*' for him, but despite this appearance of stiff formality they were good friends to the end of Rolf's life. H-Ch acknowledges his gratitude to Rolf and that he and their publications were a great help in his own career.)

Rolf then worked alone on a more comprehensive analysis of ^{45}Ca-tracer fluxes as influenced by alterations of external [Ca] and [Na] as well as beat activity (Niedergerke 1963 *a*,*b*). Many younger scientists will be astonished that over 60 pages of one edition of *J Physiol* could be occupied by the work of a single author. Rolf's paper showed an exceptional attention to critical detail, even by the different publishing habits prevalent then. Next, he focused on the action potential itself. Dick Orkand had joined him at UCL and their *Science* paper (1964) interpreted the influence of Ca on the overshoot. Two full *J Physiol* papers – once more characteristically exhaustive and detailed – followed two years later (1966*a*,*b*). In these he took great care to distinguish any *indirect* role of Ca on other current-carriers (e.g. via surface charge effects) before concluding that Ca must itself be a current-carrying ion – however minor – that contributes to the action potential.

Rolf's next collaboration, with Reg Chapman (1970*a*,*b*), provided a thorough analysis of the dynamics of the response of frog heart to changes in [Ca^{2+}] and heart rate. Their multi-compartment description of the kinetics married ideas from Rolf's extensive tracer work with by-then emerging notions on the role of superficial and internal Ca stores in excitation–contraction coupling.

In a 1971 *Nature* paper, Rolf (with David Gadsby and Sally Page) first addressed a key concept developing from contemporaneous considerations of putative Ca–Na exchange mechanisms, namely, whether *intracellular* [K] and [Na] regulate the strength of the heartbeat. The results presented in this paper did (and do) not fit easily with some proposals concerning CaNaX that were emerging around that time and soon after. Perhaps one reason for this is that few papers directly address the dynamic control of tension (as observed in Ca–Na *antagonism*) as opposed to ion fluxes and considerations of steady-state intracellular ion concentrations (more directly addressing CaNaX) where dynamics of Ca flux and Ca current can often be taken as a 'proxy' for tension (if indeed tension production is considered at all).

In what proved a rare departure from studying the heart, Rolf's 1977 paper with the two Davids –Gadsby and Ogden – addressed the electrogenic sodium pump in skeletal fibres. By this time, Rolf had already been collaborating for several years with Sally Page with whom most of his subsequent research was done. They worked together first on cardiac ultrastructure (electron microscopy being a skill Sally brought to the work) providing further concrete details on extracellular tortuosity, membrane caveolation and the disposition of the sarcoplasmic reticulum in frog heart (1972). They also refined ^{45}Ca tracer methodology to permit a still-finer time resolution of Ca fluxes associated with the cardiac action potential. These various experimental and theoretical strands underpinned their interpretation of further functional studies on the actions of caffeine, adrenaline and ATP on the heart (1981).

All this work is characterised by a painstaking approach to experimental work by conducting all conceivable controls seeking out artefacts and distortions, rounded up by the scrupulous handling of data that led to the published results. Rolf's drive for algebraic and quantitative descriptions of his results is seen frequently. Rolf's two solo papers in 1963, filling 65 pages in *J Physiol*, deserve the greatest respect on these grounds alone, even regardless of their too-often unacknowledged significance in the then-emerging 'calcium story' in EC coupling. The rigour Rolf exercised in making the steps from raw data through data interpretation to results reveals Rolf's intellectual power. Few can hope to emulate such consummate experimental practice. Ted Johnston used to remark that, after pondering and researching a physiological question through theorising and scholarship, he 'would be forced to go into the lab'. Any reading of Rolf's papers gives the impression that Rolf did his thinking as much in the laboratory as outside it.

Lest Rolf the man is lost in this description of his pioneering academic life, Sally Page has reminded us that Rolf's dry humour was a constant feature of his personality, often displayed in lab teaching and in private life. Outside science, Sally and Rolf travelled widely together, combining walking in hills and mountains (Europe, Turkey, North Africa, Madeira) with exploring old towns and museums. In London, weekly museum and gallery visits, theatre and concerts provided Rolf's relaxations; walking, reading and music were his Sunday occupations. As Don Jenkinson noted "*those privileged to know him well came to appreciate his unobtrusive kindliness and the breadth of both his scholarship and interests (especially in European history and art*)." Rolf's health deteriorated in the last few years of his life, most cruelly robbing him of his sight and his power of speech. After a brief bout of pneumonia, Rolf died peacefully on 27 December 2011 at the Royal Free Hospital, London.

Rolf received the first *Rudolf Buchheim Prize* of the German Pharmacological Society and was made an Honorary Member of The Physiological Society in 1987, on his retirement as Reader in Physiology at UCL. Despite a long and illustrious career, Rolf Niedergerke published fewer than 50 papers. To present-day workers this will seem a modest total (though 'pages-per-author' perhaps less so!). However, ten of Rolf's works have each been cited more than 100 times (at an average of 275 by March 2012). Surely, a strong case can be made that his work was far more influential than even this impressive citation rate attests. There is no doubt that Rolf's intellectual and experimental excellence provided keystones of much of our present understanding of the role of cellular Ca in muscle contraction and cardiac EC coupling, of the Ca–Na exchange process as well as in what will always be seen as a crowning achievement of cell physiology: the collaboration that revealed the sliding filament mechanism of muscle contraction.

Hans-Christoph Lüttgau & David Miller

Photo: Don Jenkinson, SM Padsha, Otto Hutter, Christoph Lüttgau, Rolf Niedergerke (on the roof of UCL Physiology, *ca* 1956; taken by Keith Copeland of the electronics workshop)

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