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EDITORIAL

Hodgkin and Huxley and the basis for electrical signalling: a remarkable legacy still going strong

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The initiation and propagation of electrical signals in nerves and other excitable tissues have fascinated physiologists for well over a century. For much of the first half of the twentieth century the prevailing explanation for the depolarization occurring during an action potential was that of 'membrane-breakdown' suggested by Bernstein in 1902. He proposed that at rest the cell membrane was selectively permeable to K^+ ions, which would tend to diffuse out of the cells down their electrochemical gradient and maintain a negative resting membrane potential. According to this model an action potential was then triggered by a transient increase in permeability for all ions and hence the cell membrane potential would approach zero. In the late 1930s and early 1940s Curtis & Cole (1942) in the United States and Hodgkin & Huxley (1939) in the United Kingdom, provided definitive evidence that during an action potential the membrane potential greatly exceeded 0 mV. This was inconsistent with the 'membrane-breakdown' hypothesis but rather suggested that during depolarization the membrane was still selectively permeable to some ions, but clearly not K^+ ions.

Between 1946 and 1952, Hodgkin and Huxley, initially in collaboration with Bernard Katz, set about using the newly developed voltage-clamp technique, to dissect the basis of the changes in selective permeability that occur during propagation of action potentials in the squid giant axon. This culminated in the publication of five seminal papers in *The Journal of Physiology* in 1952. The first four experimental papers, published back-to-back in April 1952, described (i) the measurement of current–voltage relationships in the membrane of the squid giant axon (Hodgkin *et al.* 1952), (ii) basic characteristics of the currents carried by sodium and potassium ions (Hodgkin & Huxley, 1952*a*), (iii) the effect of varying the time and duration of depolarization and repolarization steps on the different components of membrane current (Hodgkin & Huxley, 1952*b*), and (iv) the 'inactivation' process which gradually reduces sodium permeability after it has undergone the initial rise associated with depolarization (Hodgkin & Huxley, 1952*c*). In the final of the five papers, published in August 1952, Hodgkin and Huxley synthesized their results by providing a 'quantitative description of membrane current and its application to conduction and excitation in nerve' (Hodgkin & Huxley, 1952*d*). This final paper is still one of the most elegant examples of computer modelling in biological sciences. The frequency with which it is cited (over 9000 times in total and over 300 times in the last 12 months alone) is testament not just to the fact that it represents a genuine paradigm shift in the study of membrane physiology and electrical signalling but also to its incisive logic and clarity of presentation. It truly is a must read paper even more than half a century on.

Although 60 years have passed since these pioneering papers were published, they still stimulate research in almost all branches of physiology and its modern descendent, 'systems biology'. They have also stimulated research at the most fundamental level, ranging from atomic resolution structural analysis of ion channels, through to innovative clinical research that may soon deliver new therapies for disorders of excitability. To celebrate the 60th anniversary of the '1952 Hodgkin Huxley papers', we have included in this special issue a series of reviews that reflect on both the historical significance and the modern legacy of their work. We start with a historical overview (Schwiening, 2012), followed by overviews of sodium channels (Catterall, 2012) and potassium channels (Jan & Jan, 2012) and how the pioneering work of Hodgkin and Huxley continues to inspire work on these channels. This is followed by a review that examines the clinical significance of the Hodgkin–Huxley legacy and sodium channelopathies (Waxman, 2012). Lastly we have an overview on computer modelling of the heart (Noble *et al.* 2012), a remarkably productive area of systems biology research, which can trace its origins directly to the work of Hodgkin and Huxley. In addition to this special focused issue, *The Journal of Physiology* has released a special online-only issue in which the original 1952 papers are available along with a selection of the many hundreds of papers inspired by the work of Hodgkin and Huxley and subsequently published in *The Journal of Physiology* (see http://jp.physoc.org/site/misc/virtualissues_archive.xhtml)

Looking forward, we expect that the Hodgkin–Huxley contribution will continue to propel biomedical research, in areas as diverse as muscle physiology and pharmacology, autonomic physiology, neuroscience, disease pathophysiology and even clinical medicine.

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