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Memories of a Senior Scientist

50 years of passionate commitment

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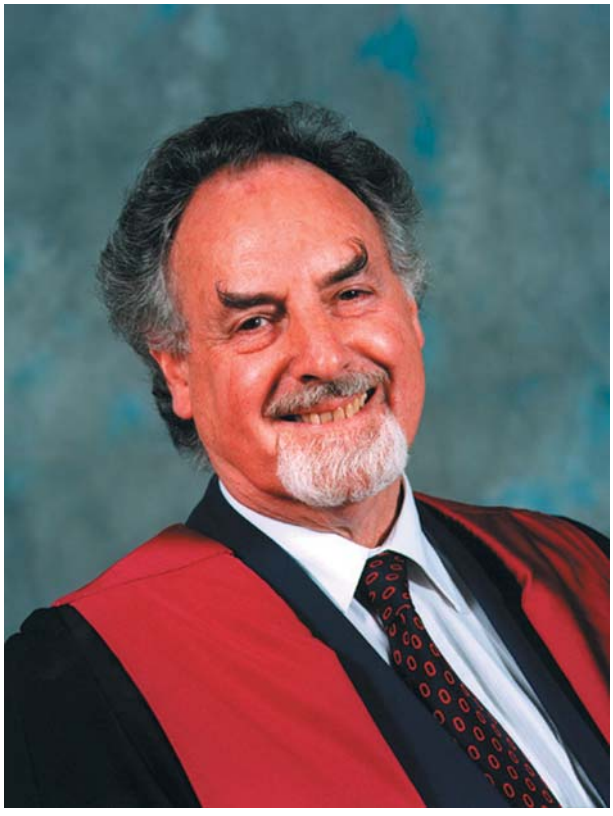

Introduction

I have been invited to introduce this fragment of autobiography by Geoffrey Burnstock. This is a titillating morsel while we wait for the main course (which I hope he is working on). I had the privilege of being a colleague of Geoffrey's for a few years at University College London. So, from first hand experience, I can describe him in one word – effervescent.

I can also make three claims for his achievements as a scientist.

First, his investigations have not been based on the development of new technology. His style has been to use established techniques to probe new questions and new ideas. The remarkable feature of his work has been the range of techniques that he has brought to bear on his lifetime's interrogation of how the visceral nerves work, the neuro-effector systems. He has imported techniques and ideas from histology, electrophysiology, in-vitro pharmacology and comparative physiology. He must be one of the pioneers of the multi-disciplinary research that is so fashionable today.

Second, his work has changed the way we think about neuro-effector control mechanisms. Having lived through each of his radical discoveries, I can testify to the reluctance and pain of having been forced by him to discard some of my long-held concepts. As far as I can see, in biomedical science most of the new knowledge we acquire adds on to or amplifies the existing stock: new knowledge that is incompatible with the old, that is, after Kuhn, a paradigm shift, is rare. Remarkably, he has contributed three of them.

Third, I associate his contributions to Burnstock as an individual. Although he has always had colleagues (indeed he must rank high as a post-graduate teacher), the ideas that his work has generated seem to be uniquely his own. Moreover, all his ideas met with considerable opposition at their introduction. Consequently, the gradual acceptance of his ideas has been the result not only of his huge appetite for experimenting and publishing but also for his

courage and exuberance in single-handedly taking on the opposition.

Burnstock's concepts are now universally accepted and they have been incorporated in to the hard core of physiology.

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50 years of passionate commitment

I was into **challenging accepted doctrines** from an early age. At grammar school, as a prefect, I was asked to address school assembly. These addresses were usually based on religion, however, since I was already an avowed agnostic, I gave my address on 'humour', one of the few topics that I knew I definitely believed in; this led to staff debate and nearly to my expulsion. Later as an undergraduate, I was the co-founder of the Sceptic Society that met regularly in a pub in Fleet Street in London. Its membership was made up largely of physicists, biologists and historians earnestly seeking ways to make moral decisions without involving either religious or political solutions. Looking back, I realise that this was only one of the early character traits revealed in my school and undergraduate days that were later reflected in my approach to research. **Infectious enthusiasm.** I was a passionate table tennis player and soon the school staff as well as the students were heavily involved in this game much of the time, to the extent that I was called in by the headmaster and reminded that school was about scholarship, not table tennis. A feature of my later research career seems to have been to inspire postgraduate students and collaborators. I have supervised over 100 PhD and MD students and at a Festschrift Meeting in 2000, it was pointed out that I had published with over 850 co-authors. I am still working hard and so these figures will be increased. **Overcoming obstacles**. I tried unsuccessfully to get into medical school in the late 1940's and early 1950's, even though my academic record was OK, in retrospect probably because of my modest background in a class conscious culture. My father ran away from home aged 15 and pretended to be old enough to join the army to serve in the first World War, was wounded in the battle of the Somme and given a postwar job as a temporary clerk in the civil service. He died when I was 17 years old, but always encouraged me to get educated. After completing my National Service in the Airforce, I missed out by one day being awarded an ex-service University Scholarship and had to spend much of my weekends and evenings working in a graveyard to make enough money to allow me to study and look after my mother. In later life I always followed the principle that if things do not work one way, try another and another…. Sometimes a rejection that was depressing at the time was followed by an alternative that turned out to be a better solution. **Asking meaningful questions.** A memorable experience during my early training in the airforce was being in a wooden hut with about 160 other lads and being told by the Corporal "outside in the road in threes, last man out on fatigues". Naturally, there was a rush to get out and the front of the hut was smashed down. A furious young officer asked us 'who is responsible for smashing the hut?' I asked myself did he mean the man in front, the Corporal for giving the order, or even the basic airforce disciplinary philosophy and I was marched off for 'laughing on parade'. Nevertheless, this taught me the important lesson that I have used in later scientific life, namely that asking a well thought out, meaningful question is the starting point for all good research. **Recognising your strengths and weaknesses.** At one stage early in my life, I was highly motivated to become a great flamenco guitar player. I went to Spain to learn how to play and my teacher said after a year or so that I should go down to the village after dinner and play; if they liked my playing, the girls would dance. Sadly, no-one danced, and I had to face the fact that I was not up to it! It made me realise that we all have limitations and that I should try to take up other activities where I could make better use of my strengths – so, I decided to have a go at Science.

My early scientific experience in research was a mix of disciplines, undergraduate Zoology at Kings College London, postdoc experience in the Department of Physiology at the National Institute of Medical Research at Mill Hill, the Department of Pharmacology, Oxford, and then in the Department of Physiology and Biophysics, Champaign-Urbana. I liked the Australian scientists such as Mike Rand and Mollie Holman, that I worked alongside in these early years, so that I decided to try for my first academic post in Melbourne, where I was appointed as a Senior Lecturer in Zoology in 1959 and promoted to Professor and Chairman of Department in 1964. I was invited to return to England in 1975 to take over from J.Z. Young as Head of Anatomy and Embryology at University College London.

My approach to research has been to explore systems in a multidisciplinary, lateral-thinking kind of way. This led to several radical hypotheses that sometimes challenged established concepts and inevitably met with strong resistance and disbelief. However, as I passionately pursued them, together with my students, scientific and medical colleagues, in time some of these hypotheses have become accepted. This approach requires 'intuition' as well as factual information and, while I have been criticised for this, I believe that intuition is a rich source of subconscious information and an advantage for use particularly by scientists with a long-term background in a field.

The focus of my research interest in those early years was smooth muscle and its innervation, and the first important conceptual break came in the early 1960's when, together with my students Graeme Campbell and Max Bennett in Melbourne, we discovered autonomic neurotransmission that did not involve either the classical transmitters acetylcholine or noradrenaline. This was an accidental finding, in that a puzzling rapid hyperpolarisation of intestine smooth muscle remained after blocking classical transmission with adrenergic and cholinergic antagonists; this hyperpolarisation was later blocked by tetrodotoxin, revealing that it was an inhibitory junction potential in response to non-adrenergic, non-cholinergic (NANC) inhibitory nerves. Recognition of NANC excitatory transmission in bladder and blood vessels soon followed and we set out to find the transmitter involved. Based on the criteria established by Eccles and others at that time to establish the existence of a neurotransmitter, we came up with the surprising answer that it was ATP. Since ATP is a purine nucleotide, I decided to call this new type of neurotransmission 'purinergic' and in 1972 published what has become a classic paper in Pharmacological Reviews entitled 'Purinergic Nerves'. This was followed for over 20 years by a lively controversy, with the majority rejecting the concept on the grounds that ATP was an intracellular source of energy in all cells and therefore too ubiquitous a molecule to be a neurotransmitter. I was attacked and ridiculed at international meetings and, amazingly, several people said they would 'devote their lives to destroying the purinergic hypothesis'! My own view was that as a primitive biological molecule, ATP was utilised both as an intracellular energy source and an extracellular signalling molecule early in evolution. This view has been supported by studies of purinergic signalling both in invertebrates and lower vertebrates, as well as during embryological development.

In 1978, I recognised that receptors for purine nucleotides, ATP and ADP, could be distinguished from receptors for their breakdown product, the purine nucleoside, adenosine, but it was not until the early 1990's that people began to believe in the purinergic hypothesis. Together with my old friend Eric Barnard, we cloned the first G protein-coupled receptor for ATP ($P2Y_1$) at about the same time as the laboratory of David Julius in San Francisco cloned the $P2Y_2$ receptor. A year later, the first two ATP ionotropic receptors ($P2X_1$ and $P2X_2$) were cloned. Subsequently, seven P2X and eight P2Y receptor subtypes have been cloned and characterised. Evidence was also presented in 1992 for purinergic synaptic transmission in the brain. These two discoveries were the turning point and there is now wide recognition of purinergic signalling in both neuronal and non-neuronal cells and outstanding colleagues in many laboratories around the world are making major contributions to this field. When I look for PhD students or collaborators, I hope firstly to see signs of passionate commitment and courage and only secondly for intelligence and technical skill. Good judgement is also a key factor for success, but this takes time to reveal itself.

Another hypothesis that met initially with strong resistance and even anger was the Commentary entitled 'Do some nerve cells release more than one transmitter?' that I published in Neuroscience in 1976, soon after returning to the UK. In this paper I pulled together a number of examples from both the invertebrate and vertebrate literature, with enough anomalies to challenge what had become known as 'Dale's Principle': that one nerve only releases one transmitter (although Sir Henry Dale himself did not actually say this). However, today it is well established that all nerves in the peripheral and central nervous systems utilise more than one transmitter, so that the terms adrenergic, cholinergic, peptidergic, purinergic, nitrergic or glutaminergic nerves are no longer acceptable, although these terms are still meaningful to describe neurotransmission.

I have put forward two further concepts in more recent years: The first is a follow-up of the brilliant discovery by Bob Furchgott about endothelial-derived relaxing factor (EDRF) and its identification as nitric oxide (NO). Part of this story was that neurotransmitter molecules like acetylcholine, substance P, ATP and others, act on receptors on vascular endothelial cells to release NO, resulting in vasodilatation. The assumption by many in the cardiovascular field has been that the transmitters acting on endothelial cells originate from perivascular nerves. It became clear that in all vessels, except microvessels, transmitter released from nerves would never survive enzymatic degradation while diffusing through the medial muscle coat and elastic lamina to reach the endothelial cells. What my colleagues, in particular Andrew Loesch, showed was that these transmitter molecules were synthesised and stored in endothelial cells and released by shear stress during changes in blood flow and during hypoxia.

The second and most recent hypothesis that seems to be gaining recognition is purinergic mechanosensory transduction. This is a simple concept that says that mechanical distortion (for example, as the result of distension of visceral organs such as ureter, intestine and bladder) leads to release of ATP from epithelial cells that act on $P2X_3$ nociceptive receptors on subepithelial sensory nerve terminals to trigger responses that relay through sensory ganglia and through the spinal cord to pain centres in the brain or set up local physiological reflexes like bladder voiding or gut peristalsis.

In the early days, I did my research largely to satisfy my own creative spirit, rather I suspect like artists work, without any altruistic objective. However, in my later years I feel it would be nice to do something 'useful' before I am gone, and so I have been working more and

more in collaboration with clinicians and the pharmaceutical industry to explore whether there is some therapeutic potential to the basic science I have pursued for most of my working life.

Sometimes when I visit laboratories these days, I am tempted to say that however intelligent and technically brilliant the work is, one must not forget that it should be enormous fun to do, a joy to work together with equally passionate and committed colleagues, and never to forget what a privilege it is to do science, when every day there is the possibility of making a new and exciting discovery.

Some key papers

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