A moment of excitement

To launch our *Living History* series, Geoffrey Burnstock recalls the discovery of non-adrenergic, non-cholinergic autonomic neurotransmission

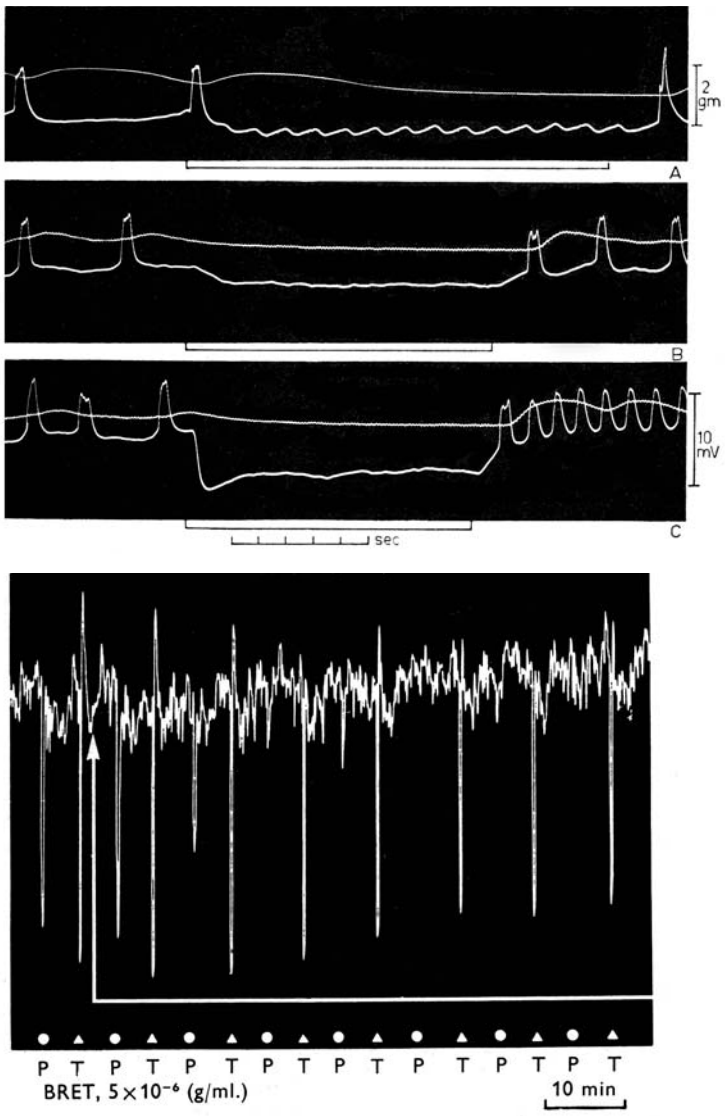
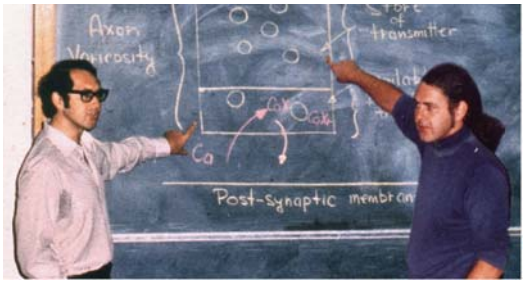


Figure 1 (top). Sucrose gap records from smooth muscle of guinea pig taenia coli showing inhibitory potentials in response to stimulation of intrinsic nerves. Frequencies of stimulation: (A) 1/sec; (B) 10/sec; (c) 20/sec. Upper trace, tension; lower trace, membrane potential. Note the phase of excitation (B and C) which follows cessation of stimulation (from Burnstock, Campbell, Bennett & Holman (1963). *Nature* 200, 581-582)

Figure 2 (above). Effects of adrenergic neurone-blocking drugs on responses to stimulation of the taenia or of the perivascular nerves after atropine. Perivascular nerve taenia preparation. Bretylium (BRET, $5x10^{-6}$ g/ml.) abolished mechanical responses to stimulation of the perivascular nerves at 30 pulses/sec (P, at dots), but only reduced responses to stimulation of the taenia with 10 pulses/sec (T, at triangles). Time marker 10 min (from Burnstock, Campbell & Rand (1966). *J Physiol* 182, 504-526)



Max Bennett (left) with Graeme Campbell, about 1983

I remember vividly the day that we discovered non-adrenergic, non-cholinergic autonomic neurotransmission.

Together with Ralph Straub at the National Institute of Medical Research, the sucrose gap technique for recording continuous, correlated changes in electrical mechanical activity of smooth muscle was developed (Burnstock & Straub, 1958). I moved to Edith Bülbring's lab in the Department of Pharmacology, Oxford, and completed studies of classical adrenergic and cholinergic responses of the guinea-pig taenia coli (Burnstock, 1958a,b).

From Oxford, I moved to Melbourne, Australia where, with the help of an NIH grant held jointly with Mollie Holman, whom I had met in Oxford and whose work I had admired there, I set up the sucrose gap apparatus in my laboratory.

Graeme Campbell, a postgraduate research assistant and Max Bennett, at that time a part-time electronic technician who was completing a degree in Electrical Engineering, were working with me, and one day in 1962 we decided to look at the direct responses of the smooth muscle of the taenia coli after blocking the responses of the two classical neurotransmitters, acetylcholine and noradrenaline. Graeme and Max came into my office to show me the remarkable responses to stimulation, which were rapid hyperpolarisations and associated relaxations in response to single electrical pulses. This was a very exciting moment – we all felt instinctively that this unexpected result was going to be important.

Later we, and others, showed that tetrodotoxin, which had just been discovered in Japan and which blocked nerve conduction but not muscle responses, abolished these hyperpolarisations and we realised that we were looking at inhibitory junction

potentials (IJP's) in response to a non-adrenergic, non-cholinergic (NANC) inhibitory neurotransmitter (Burnstock *et al.* 1963, 1964). This was followed by a detailed study of the mechanical responses of the taenia coli to stimulation of intramural and sympathetic nerves while I was on sabbatical leave at the School of Pharmacy in London, working together with my friend Mike Rand (Burnstock *et al.* 1966). Nearly a decade later, after much work, we published a paper that suggested that the NANC transmitter in the taenia coli was ATP (Burnstock *et al*. 1970).

Geoffrey Burnstock

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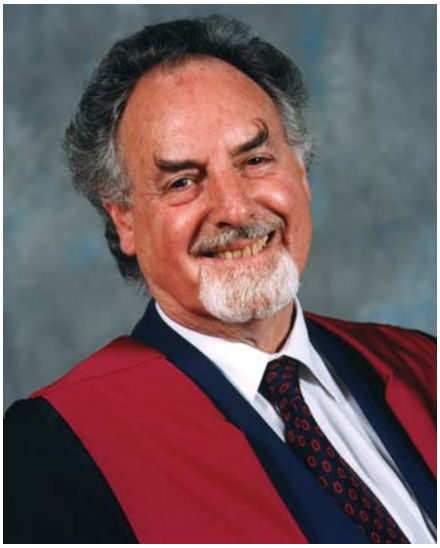
Above
Top: Mollie Holman and Geoff Burnstock, 1960
Above: Edith Bullring and Geoff Burnstock, about 1985

Right: Geoff Burnstock in 2003

Below:
Left: Geoff Burnstock with Mike Rand, about 1992



Biographical notes about all those featured in the article appear on the next page

Biographical notes

Ralph Straub *was a visiting scientist in Feldberg's Department at the National Institute of Medical Research in the late 1950s. He returned to Switzerland in the 1960s to become Professor of Pharmacology at the Centre Médical Universitaire, Geneva. He died in April 1988 when only 60 years old.*

Edith Bülbring *was born in 1903 in Bonn. She joined the Department of Pharmacology in Oxford in 1937 and between 1950 and 1990, when she died, established her laboratory as the leading international laboratory in smooth muscle pharmacology and physiology; she had a major influence on many working in this field today.*

Mollie Holman *was born in 1930 in Australia. She joined Edith Bülbring's group in Oxford to work on the electrophysiology of smooth muscle, completing a DPhil in 1957, and then returned to Melbourne and was eventually appointed as Professor of Physiology at Monash University. She retired in 1995.*

Graeme Campbell *was born in Australia and completed a PhD in Zoology supervised by Geoff Burnstock in 1965. In 1976 he took over the Chair of Zoology in Melbourne vacated by Geoff Burnstock on his move to UCL Anatomy, but is now retired.*

Max Bennett *was born in 1939, completed a degree in Engineering in 1963 and switched to Zoology, completing a PhD in 1967 under the supervision of Geoff Burnstock. He was appointed as a Lecturer in Physiology at Sydney University in 1969 and rose to Professor of Physiology in 1983. He is now one of the most active and distinguished neuroscientists in Australia.*

Mike Rand *was born in 1927 in England, but moved with his mother to Australia in 1941. He completed his PhD in Pharmacology in Sydney University and then accepted a postdoctoral position in Oxford Pharmacology with J.H. Burn in 1957. After a period of 5 years at the School of Pharmacy in London he accepted the Chair of Pharmacology in Melbourne University in 1965 and after 'retirement' took up an appointment as Adjunct Professor at RMIT University, also in Melbourne. He was a marvellous scientist and had a major international influence; sadly, he died in 2002.*

Training and competition stress: effects on immune function and health

Mike Gleeson continues our series of articles on exercise physiology in the run up to the Olympics by considering the health implications of hard training by endurance athletes

Mike Gleeson

Athletes dread the thought of catching a cold or the 'flu. Infections can interfere with training, impair performance and even prevent an athlete from competing. Unfortunately, athletes engaged in heavy training programmes, particularly those involved in endurance events, appear to be more susceptible than normal to infection. For example, several epidemiological studies in the 1990s indicated that sore throats and flu-like symptoms are more common in endurance athletes than in the general population. The immune system protects the body against infection but the functioning of the immune system is affected by stress and there is some evidence that the increased susceptibility to infection in athletes actually arises from a depression of immune function. Although impairment of immune function sometimes leads to the reactivation of a latent virus, the development of a new infection generally requires exposure to a pathogen, and there are many training and competitive situations in which the athlete's exposure to pathogens is increased.

Heavy prolonged exertion is associated with increased levels of stress hormones (e.g. adrenaline and cortisol) and cytokines (e.g. interleukins 6 and 10) which inhibit some aspects of immune function. Several changes during early recovery from exercise would appear to weaken the potential immune response to pathogens and although the clinical significance of these changes has not been established, it has been suggested that the post-exercise period may provide an 'open window' for infection representing the most vulnerable time for athletes in terms of their susceptibility to infection. The impairment of immune function following a prolonged bout of exercise is associated with decreased expression of the Toll-like receptors on monocytes that detect pathogens, decreased killing capacity of neutrophils and natural killer cells, decreased cytokine production by type 1 T-helper cells together with the disappearance of these lymphocytes from the circulation, decreased lymphocyte proliferative responses to antigens and increased apoptosis under the influence of cortisol. The secretion of cortisol during exercise is stimulated by muscle-derived interleukin-6 (IL-6). Studies from Bente Pedersen's group in Copenhagen indicate that the release of IL-6 from contracting muscle can be attenuated by carbohydrate ingestion during exercise and by long-term antioxidant supplementation. This group has argued that this, however, may be a two-edged sword, as IL-6 has several metabolic effects and shared mechanisms exist regarding immune impairment and training adaptation. The concern for athletes is that although these nutritional interventions may reduce their risk of infection, another effect may be to limit their hard-earned adaptation to training.

Figure 1. Monitoring of saliva immunoglobulin A in swimmers can provide an idea of mucosal immunity