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Geoffrey Burnstock was a biomedical scientist who gained renown for his discovery that adenosine 5'-triphosphate (ATP) functions as an extracellular signalling molecule. Born in London and educated at King's and University colleges, he did postdoctoral work at Mill Hill and Oxford. He moved in 1959 to the Department of Zoology at the University of Melbourne because he sensed there a greater freedom to challenge established thinking in physiology. His group found that transmission from sympathetic and parasympathetic autonomic nerves to smooth muscle was in some places not mediated by the accepted chemical messengers (noradrenaline and acetylcholine). He amassed evidence that ATP was this non-adrenergic, non-cholinergic transmitter, using biochemical, histological and electrophysiological approaches: heretically, he styled this 'purinergic transmission'. Geoff further upset dogma in the 1970s by proposing 'co-transmission' in which some nerves released ATP in addition to either noradrenaline or acetylcholine. He distinguished pharmacologically P1 receptors (activated best by adenosine and blocked by xanthines) and P2 receptors (activated best by purine nucleotides such as ATP) and he proposed in 1985 that the latter embraced P2X (ion channel) and P2Y (G protein-coupled) subtypes: about 10 years later these categories were substantiated by cDNA cloning. From 1975 until his retirement in 1997, Geoff was head of the Department of Anatomy and Embryology at University College London (UCL), which he developed energetically into a large and strong research department. Later, as head of the Autonomic Research Institute at the Royal Free (part of UCL), he continued to collaborate extensively, and founded several journals and international professional societies. He widely sought clinical benefit for his discoveries, and both P2X and P2Y receptors have been developed as the targets of useful therapeutics (gefapixant, clopidogrel). Geoff was

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proud of his modest, rather humble, background and eschewed formality. He may have smiled when his early discoveries were met with cynicism, even ridicule ('pure-imagine' transmission noted one amusing critic), but this just reinforced his resolve and encouraged his encyclopaedic oeuvre.

## EARLY YEARS AND EDUCATION

Geoffrey Burnstock was second of the two children of James and Nancy Burnstock. His father Jim came from a large working-class family in the East End of London; several of the nine sons were boxers. Jim ran away from home aged 14, enlisted, and fought at the Somme, where he sustained serious lung injuries. Nancy was the daughter of Wolf and Sarah Greenberg, who belonged to an artistic and intellectual Jewish family that immigrated to London from the western part of what is now Belarus.

Geoff was born on 10 May 1929 on Portobello Road. He grew up in Ealing, and he attended the Greenford County School (now Greenford High School, which opened as a grammar school in 1939). He recalled teenage years with his father during the blitz. Geoff applied to, and was rejected by, several medical schools because 'I had the wrong accent, clothes and school background' (27)\*. His two-year period of national service in the Royal Air Force was shortened to allow him to matriculate at Kingston Technical College (now Kingston University London); however, with further A levels in mathematics and physics, he was again declined entry to medical school. His father died in 1948 and Geoff helped to support the family by working night and weekend shifts in the local graveyard.

In 1950, King's College London (KCL) accepted him into their Associateship of King's College (AKC) programme in theology (although Geoff was a life-long atheist), but later allowed him to include zoology; he completed both courses and was awarded the BSc in 1953. His PhD studies began at King's, where he developed a method to study intestinal movements in the brown trout (1); he later transferred to the supervision of J. Z. Young FRS in the Department of Anatomy and Embryology at University College London (UCL). At KCL, Geoff initiated discussion meetings at the interface of art, science, history and religion, together with contemporaries including Eric Barnard (FRS 1981) and Lewis Wolpert (FRS 1980).

As he was finishing his PhD at UCL in 1957, Geoff met Nomi Hirschfeld, and they subsequently married in 1959. Nomi was the daughter of Sigi and Gisi Hirschfeld, secular Jews originally from Vienna, who had emigrated from Palestine to New Zealand in 1940.

In a first postdoctoral position, Geoff worked in the laboratory of Wilhelm Feldberg FRS at the National Institute for Medical Research at Mill Hill. At Mill Hill, Geoff met Ralf Straub, who was visiting from Robert Stämpfli's laboratory in Bern. Stämpfli had developed the sucrose gap method to record the membrane potential of nerve fibres (Stämpfli 1954); Burnstock and Straub applied it to the taenia coli (2). The movements of the intestine result from coordinated contractions of two layers of muscle in its wall, and at that time there was controversy about any role for the nerves in initiating and propagating peristalsis. In some places and in some species, such as the caecum of the guinea pig, the longitudinal muscle layer is collected into three narrow strips, the taenia coli.

At that time, Edith Bülbring (FRS 1958) was the doyenne of smooth muscle physiology and, having seen Geoff's technique, she invited him to join her group in Oxford. The

<sup>\*</sup> Numbers in this form refer to the bibliography at the end of the text.

young Australian Mollie Holman was then in Bülbring's laboratory studying for her DPhil by making intracellular recordings from intestinal smooth muscle *in vitro* with fine glass micro-electrodes, a non-trivial task given the spontaneous movements of the muscle. The combination of these recordings with Geoff's sucrose gap technique provided a sharp increase in our understanding of the electrical activity and contraction in smooth muscle (3); they also showed that acetylcholine depolarized and contracted the muscle (4), whereas noradrenaline hyperpolarized the membrane and inhibited spike activity (5).

A Rockefeller Travelling Fellowship allowed Geoff to visit Ladd Prosser's laboratory in Illinois for several months in 1959, as well as to travel to other laboratories in the USA (such as the Marine Biology Laboratory at Woods Hole, Massachusetts). While in the US he had to decide whether to stay there, or to return to Oxford as a research fellow, but, as he later described, 'the people I liked most in Oxford were Australians, so I decided instead to apply for a job in the Department of Zoology in Melbourne University. Also I had married Nomi, who had lived in nearby New Zealand, and it was attractive to escape class-conscious England and enjoy the positive Australian approach to new initiatives ("give-it-a-go, mate")'(27).

## ZOOLOGY AT THE UNIVERSITY OF MELBOURNE

Geoff arrived at the University of Melbourne in October 1959, taking up a position as senior lecturer in the Department of Zoology. He was recruited by Mike White, then chairman of the department. Mollie Holman, who had been appointed to a lectureship in the Department of Physiology the previous year, had been enthusiastic in supporting an offer to Geoff. Mollie wanted to move to a smooth muscle preparation that was not spontaneously active, which greatly facilitates intracellular microelectrode recording. Mike Rand had been working in the Department of Pharmacology at Oxford with Joshua Burn FRS in the late 1950s; while visiting Melbourne, he showed Mollie and Geoff how to dissect out the vas deferens from the guinea pig, with its sympathetic nerve attached (the hypogastric nerve). In a collaboration with Geoff, in 1960 Mollie first recorded the excitatory junction potential (EJP) in the smooth muscle of the vas deferens (6) (figure 1). Mike Rand became professor of pharmacology at the University of Melbourne in 1965 and remained a close colleague of Geoff's. Mollie Holman moved to a senior lectureship in physiology at Monash University in 1963, which had just opened its doors to students in March 1961.

A critical period in the history of purinergic research, which came to represent the major scientific contribution of Geoff Burnstock's life, started in 1961. The intracellular recordings from the vas deferens continued in the Department of Physiology, where Geoff and Mollie were assisted on a part-time basis by Max Bennett, an undergraduate student of electrical engineering at Melbourne. Geoff had learned the sucrose gap method during his time at Mill Hill and Oxford, and in 1961–1962 this was established in the Department of Zoology. It was initially used by Max Bennett to study the smooth muscle of the ureter (Bennett 1997), and in 1962 Max became Geoff's MSc (and later PhD) student.

Max was joined by Graeme Campbell, another PhD student of Geoff's, to apply the sucrose gap method to the taenia coli, now modified to allow electrical stimulation. The first evidence for the presence of inhibitory transmission in the intestine came in December 1962. When the taenia coli preparation was stimulated electrically, a transient hyperpolarization was observed after a delay of about 200 ms; this was called an inhibitory junction potential (IJP) by analogy with the EJP seen in the vas deferens. The findings were communicated to the Australian



Figure 1. Mollie Holman and Geoff Burnstock examining oscilloscope film, Melbourne, about 1960. Credit: Burnstock family.

Physiological and Pharmacological Society in Canberra in February 1963. Mollie Holman, in the adjoining Department of Physiology, confirmed the observations with intracellular recording, and in November 1963 a short note was published in *Nature* (7). This discovery was totally unexpected, and there was no mention of it in reviews by Burnstock and Holman (8) and by Burnstock, Holman and Prosser (9) published earlier in 1963. Paradoxically, as Graeme Campbell noted in his thoughtful recollections of these early times (Campbell 1970, 1991), Bülbring, Burnstock and Holman had already observed IJPs in their recordings from the taenia coli in Oxford, but without realizing it (3).

The next important steps in the characterization of inhibitory transmission to the taenia coli came from the use of drugs that blocked transmission mediated by noradrenaline. John Gillespie had shown in 1962 that repetitive stimulation of the sympathetic nerves hyperpolarized stretched smooth muscle of the rabbit colon (Gillespie 1962); but the IJP of the taenia coli was unaffected by drugs known to block noradrenergic transmission (10–12). In parallel, good evidence was provided that these non-cholinergic, non-adrenergic (NANC) neurons were also able actually to relax the intestinal smooth muscle (13). From then, the hunt for the identity of the transmitter of the NANC inhibitory neurons gathered pace. Graeme Campbell probably had the first suspicion that ATP could be a good candidate, because he had shown that extracts from tissues that possessed a rich NANC innervation, such as the stomach (Campbell 1966, 1969), relaxed the taenia coli and that the most powerful component of these extracts was ATP (Campbell 1970). At that time, ATP was widely known as a carrier of energy within eukaryotic cells (Kalckar 1941; Lipmann 1941), but its further role in the phosphorylation of intracellular proteins such as enzymes, transporters and receptors was barely recognized (see Cohen 2002).

In 1969 Geoff appointed David Satchell for his expertise in detecting purines by chromatography. Together they showed that stimulation of the NANC nerves to the guinea pig and toad stomach did not release ATP into the vascular perfusate; however, it released adenosine and inosine, the same substances that appeared in the perfusate if ATP itself was flowed through the stomach in the absence of nerve stimulation. Testing for a direct action of these and related substances to relax the taenia coli showed that the most potent of them were ATP and ADP, establishing ATP as a very likely NANC transmitter. The first results were communicated by David Satchell at a meeting of the Australian Physiological Society in August 1969 (14) and the work was published in full in December 1970 (15). Thus, the purinergic hypothesis of the NANC nerves was born (16, 17).

Geoff maintained his strong and productive drive to prove the purinergic nature of the NANC inhibitory neurons in the gut until he left Australia to return to UCL in 1975. However, even during the most exciting period of discovery of a new class of neurons and a novel neurotransmitter, Geoff remained interested in a multitude of aspects of the autonomic nervous system, including comparative aspects of the enteric nervous system of fish, which had started his career (1). He attracted to his lab a plethora of young researchers from various walks of life and with many disparate interests, whom he fostered and followed with genuine concern. Appointed as professor and head of department in 1964, he created a truly multidisciplinary organization filled with critical minds who, by and large, worked in parallel fields further away from the NANC neurons and retained a healthy scepticism of the purinergic hypothesis. Yet Geoff remained a close mentor of all those colleagues, and he often reminisced with nostalgia of those early times at the zoology department in Melbourne. His knowledge of the autonomic nervous system was comprehensive, spanning approaches through tissue culture, histochemistry, ultrastructure, pharmacology and electrophysiology of any organ of vertebrates and invertebrates (molluscs, fish, frogs, lizards, sheep, all small laboratory animals and of course humans). He retained this active interest in smooth muscle and its innervation throughout his career (figure 2).

## **RETURN TO UCL**

Geoff, Nomi and their three daughters (Aviva, Dina and Tammy) arrived in London in May 1975. Thus, 18 years after leaving UCL with his newly minted PhD, Geoff returned as professor and head of the Department of Anatomy and Embryology. He succeeded J. Z. Young, whose tenure of 29 years had resulted in a department regarded by Geoff as ossified in more than just the anatomical sense.

Outsiders to Oxbridge and UCL at that time could be made to feel very provincial imagine what it was like to come from somewhere quite different in culture, such as Australia. John Parnavelas recalls

the appalling way Geoff was received in the department. Everyone, to the last person, poured scorn and ridicule on him, from his Australian accent, to the way he went about doing things in his lab and department, and to his science, including the ATP hypothesis. It was really bad. Fortunately, Geoff had a thick skin that allowed him to overcome the adverse reception and to move forward both in his science and in running the department, which became the envy of all Anatomy departments in the country.



Figure 2. On the boat returning from Hayman Island Smooth Muscle meeting, Barrier Reef, Queensland, September 1983. Credit: Alan North. (Online version in colour.)

## But Geoff soon became

master of working the system in College and getting the most for the department. A demonstration of this was how he managed to appoint three of us to one lectureship that had been allocated to

#### Geoffrey Burnstock

the department in 1982. It never became clear to us how he orchestrated that, but we arrived in the department within a few months from each other and went on to build fairly successful labs.

Geoff expanded the department greatly through the next two decades. He was recognized as a tireless supporter of his staff, believing that the role of the head of department was to appoint creative people and try to provide them with an environment in which they could fulfil their potential. Another department head at that time writes:

UCL departments had a lot of independence, and a strong sense of identity and heritage. They ran their own research and teaching in an atmosphere of good-natured rivalry, with little interdepartmental collaboration and only very light touch direction from the faculty organisation. Geoff certainly treated the anatomy department as his fieldom, and he was very effective in gaining support for it.

One former colleague recalls how Geoff could never get an appointment with the university's director of finance, so he simply went very early one day and sat on the floor outside his office until he arrived.

In the 1996 Research Assessment Exercise, the department (now Anatomy and Developmental Biology) achieved the maximal 5-star rating on the basis of a submission that included every member of the permanent academic staff (52.4 full-time equivalent Category A Research staff). The teaching of human anatomy also flourished; Geoff admitted freely his ignorance of topographic anatomy, but he had the foresight to appoint dedicated senior staff to this role. When Geoff arrived in 1975 the department had three professors; when he retired in 1997 it had 26 full professors.

Bob Lieberman, the dean at that time, offered a panegyric (Lieberman 1997):

For me, without a doubt, Geoff's primary achievement has been to make Anatomy at UCL not only the biggest, but, in terms of research, the best in the UK, Europe and possibly the world. Like J.Z. before him, Geoff has nurtured the research culture of the Department and has created conditions in the Department under which individuals have been able to achieve their research potential. He has consistently recruited excellent staff and except in those cases where it was necessary to recruit for a specific teaching or other purpose, he has done so purely on merit and has not sought to direct the research of the staff along particular lines which is something that I believe has been much appreciated.

#### He continued:

Among other qualities that Geoff possesses in full measure is the ability to make his decisions emerge as though they are those of the Department as a whole. And another is to handle individuals, the carrot and the stick, so skillfully that people can emerge from meetings with him, elated and happy even though what actually happened at the meeting was that they had their teaching load doubled or their lab space halved.

## **CO-TRANSMISSION**

Since the work of Otto Loewi ForMemRS and Sir Henry Dale FRS, textbooks of physiology have ascribed chemical transmission in the autonomic nervous system to acetylcholine (preganglionic nerves and postganglionic parasympathetic nerves) and noradrenaline (postganglionic sympathetic nerves, with the exception of those supplying the blood vessels of skeletal muscle). In 1975 there was a widely held view that each nerve cell makes and

releases only one transmitter. This was sometimes called Dale's Principle, although Sir Henry Dale actually posited something else (in his Walter Ernest Dixon Memorial Lecture); namely, that all the branches of a single neuron would release the same chemical transmitter(s) (Dale 1934; Dale & Feldberg 1934). When it became clear from the work of Geoff's group in Melbourne that there was a NANC transmitter, the initial thinking was that there must be a third type of postganglionic nerve, i.e. cholinergic, adrenergic and purinergic. But one night, while on sabbatical at the University of California at Los Angeles, it occurred to Geoff that the ATP might be released by the same nerve fibres that released one of the two 'conventional' transmitters. In 1976 he asked 'Do some nerve cells release more than one transmitter?' (18) and reviewed the extensive evidence already available for co-existence of different putative transmitters in neurons.

Brownstein *et al.* (1974) had shown biochemically the co-existence of several putative transmitters in a single *Aplysia* neuron; the direct actions of peptides on mammalian neurons were beginning to come into focus (angiotensin: Barker & Nicoll 1971; substance P: Konishi & Otsuka 1974). Immunohistochemical demonstrations of novel peptide-containing nerves were starting to show the widespread presence of peptides such as somatostatin and substance P in neurons of the gut (Hökfelt *et al.* 1975a) and central nervous system (Hökfelt *et al.* 1975b). However, there was no reliable immunohistochemical marker for purinergic nerves, so Geoff redoubled his efforts to demonstrate co-transmission using functional approaches.

Consider first the vas deferens. Burnstock and Holman (6), measuring the EJP, had concluded in 1960 that 'the transmitter was most likely to be noradrenaline'. This conclusion was first called into question by Ambache & Aboo Zar (1971), who measured the twitch response and used a range of catecholamine receptor antagonists. It was known that ATP was released together with catecholamines from adrenal medullary vesicles (Carlsson & Hillarp 1956), and that ATP was co-stored with noradrenaline in vesicles from sympathetic nerves (see Smith 1972). David Westfall's group in West Virginia showed that ATP or a related purine acted as a co-transmitter (Fedan et al. 1981; Sneddon et al. 1982) by measuring both the electrical and the contractile response in the smooth muscle. Nerve stimulation evoked a biphasic contractile response, in which the fast component was blocked by  $\alpha\beta$  meATP desensitization and the slower component was blocked by phentolamine. In their experiments, the first rapid phase was mimicked by ATP or  $\alpha\beta$  meATP and blocked by a photoactivated ATP analogue arylazidoaminoproprionyl-ATP. The slower phase was mimicked by noradrenaline and blocked by the  $\alpha 1$  adrenoreceptor antagonist prazosin. Both phases disappeared after treatment with 6-hydroxydopamine, which selectively damages sympathetic nerves; thus, ATP and noradrenaline were deemed to be co-transmitters. Peter Sneddon soon moved from Westfall's group to join Geoff's laboratory at UCL and extended these observations (20) to the rat tail artery (21) and several other tissues. The relative contribution of noradrenaline and ATP to smooth muscle contraction in response to sympathetic nerve activity varies greatly among effectors (visceral and vascular smooth muscle vessels, and glands) and it is unusual for ATP to have a predominant functional role.

As for enteric purinergic neurons, Geoff had shown in 1970 that ATP was the inhibitory transmitter released by non-adrenergic inhibitory nerves in the colon (15), but he later found himself paradoxically on the defensive. Evidence began to accrue that NANC neurons in the taenia coli, which used ATP, also contained the vasoactive intestinal polypeptide (Furness *et al.* 1981). Functional studies showing that NANC inhibitory neurons in the gut utilized at

least two different neurotransmitter mechanisms (Costa *et al.* 1986) extended his very idea that neurons use more than one transmitter. With the discovery of nitric oxide (NO), a third substance present and involved in the transmission of the enteric NANC inhibitory neurons (Sanders & Ward 1992), Geoff eventually accepted that the enteric purinergic neurons had to share further transmitters, although he did not always reference the originators of such hypotheses.

## P2X AND P2Y PURINOCEPTORS

The actions of extracellular adenosine were first described in the year of Geoffrey Burnstock's birth by Drury & Szent-Gyorgyi (1929). They reported the effects of injection of adenylic acid in dogs and guinea pigs, with particular reference to effects on the heart. Incidentally, that was also the year in which ATP itself was discovered by Subbarow & Fiske (1929) at Harvard, and by Karl Lohmann (1929) in Otto Meyerhof's laboratory in Berlin (see Maruyama 1991). Adenine nucleotides were also known to have extracellular actions by the late 1970s. Cyclic adenosine 3',5'-monophosphate (cAMP) stimulated cell aggregation in the slime mould Dictyostelium discoides (Konijn et al. 1967). The effects of extracellular adenosine 5'diphosphate (ADP) were extensively studied with respect to platelet aggregation in the 1960s (Laland et al. 1961; Born 1962). Gus Born (FRS 1972) had worked on smooth muscle with Bülbring at Oxford in the 1950s (just a year or two ahead of Geoff Burnstock), but his major contributions came when he moved as professor of pharmacology to the Royal College of Surgeons in the 1960s. Born showed that extracellular ADP led to platelet aggregation, and that this effect was highly specific and likely mediated by an ADP receptor (reviewed by Flower 2020). However, the first reference to a receptor for ATP (as distinct from adenosine, cAMP or ADP) was that of Bastien Gomperts (Cockcroft & Gomperts 1979, 1980; Bennett et al. 1981; Gomperts 1983). He applied ATP (or ATP<sup>4-</sup>, as he would say, given that it was much more potent than MgATP) to permeabilize the membrane of mast cells, so that he could study the molecular machinery of histamine secretion.

Three methods were used by pharmacologists to define receptors before molecular and atomic structures were available. The first involved ranking the order the potency of a series of structurally related agonists while measuring their effects in a range of different tissues; this was used to define  $\alpha$  and  $\beta$  receptors for catecholamines such as adrenaline and noradrenaline (Ahlquist 1948). A second approach was based on the observation that certain agonists, when applied for a long time and then washed out, could prevent any further response to a brief application of agonist (desensitization). The third method was the determination of the dissociation equilibrium constant for a competitive antagonist, a molecule that bound to the receptor but did not elicit any biological effect (Schild 1974)—this method is far superior, highly quantifiable and has been widely applied, but it does require prior identification of a suitable competitive antagonist.

In a 1978 review, Geoff distinguished between P1 and P2 receptors (19). P1 receptors were activated by the purine nucleoside adenosine, and they were blocked by methylxanthines such as theophylline; these are now called adenosine receptors (A1, A2A, A2B and A3). P2 receptors were activated by purine nucleotides such as ATP but not by adenosine, and they were not blocked by theophylline. In 1985 he further separated P2X and P2Y receptors (22). The main distinguishing feature here was also the rank order of agonist potency:  $\alpha\beta$ meATP

>  $\beta\gamma$ meATP > ATP = 2-methylthioATP for P2X receptors, and the opposite for P2Y. But he also showed that  $\alpha\beta$ meATP selectively desensitized P2X receptors. By this time, it was clear that ATP (and particularly  $\alpha\beta$ meATP) could directly activate ion channel receptors through P2X receptors (Jahr & Jessell 1983; Kolb & Wakelam 1983; Krishtal *et al.* 1983) whereas ATP (and particularly 2-methylthioATP) acted at P2Y receptors through intracellular G-proteins (Dubyak & De Young 1985). We now know that one downstream effect of transduction through G<sub>q/11</sub> proteins can be opening or closing potassium channels; indeed, the former underlies the IJP of NANC transmission.

Neurotransmitter receptors of the ligand-gated ion channel (Noda *et al.* 1983) and Gprotein-coupled (Dixon *et al.* 1986) families were beginning to succumb to cDNA cloning in the mid 1980s. Although not skilled in molecular approaches, Geoff realized that his pharmacological distinction of P2X and P2Y receptors urgently required buttressing by identification of the proteins themselves, as deduced from cloned cDNAs. In 1990, he proposed to his old friend Eric Barnard FRS that they collaborate to clone a P2 receptor cDNA (see Barnard 2000). Eric had been among the first to use the *Xenopus* oocytes to express cloned cDNAs, for nicotinic acetylcholine and  $\gamma$ -aminobutyric acid receptors (reviewed by Stephenson 2020). In June 1993 (23), they reported the cloning and expression of a P2Y receptor cDNA (P2Y1), at the same time as David Julius's group in San Francisco (P2Y2: Lustig *et al.* 1993). There are now eight of these recognized (numbered 1, 2, 4, 6, 11, 12, 13 and 14); the receptor through which ADP inhibits the aggregation of platelets is now known to be the P2Y12 receptor.

In the following year, researchers at Glaxo Institute for Molecular Biology in Geneva (P2X1: Valera *et al.* 1994) and separately at the Julius laboratory (P2X2: Brake *et al.* 1994) reported the cloning and expression of the ion channel receptors for ATP. The deduced molecular properties of this receptor family turned out to be quite novel, and obviously distinct from other known ion channel receptors. Geoff quickly persuaded John Wood (FRS 2009) and other colleagues at UCL to isolate further cDNA clones using homology-based approaches, and these were published (24, 25) contemporaneously with reports from other laboratories (Lewis *et al.* 1995; Buell *et al.* 1996). There are now seven P2X receptor subunits known, which form channels usually as homotrimers but sometimes as heterotrimers (Lewis *et al.* 1995; North 2002), and eight members of the P2Y receptor family (26). The receptor responsible for the permeabilization of mast cells studied by Gomperts and colleagues is now seen to be the P2X7 receptor.

Throughout this period, Geoff redoubled his efforts to convince biomedical scientists of the importance of ATP as an extracellular signal. This strong drive could easily come over as self-promotion, but it was fuelled also by his genuine passion for discovery across a broad swathe of biomedical science. His publications were quite prolific for the subject area, reaching more than 50 per year, and indeed bore witness to his proselytizing zeal.

## LATER YEARS AT THE ROYAL FREE

When Geoff Burnstock retired from the headship of the Department of Anatomy and Developmental Biology in 1997 (figure 3), he created the Autonomic Neuroscience Institute in laboratories refurbished for him by UCL in the Royal Free Hospital. A small complement of academic staff, supplemented by several visiting fellows and students, continued the



Figure 3. In his office with wood sculpture. UCL, London, about 1997. Credit: Burnstock family. (Online version in colour.)

experimental work, while Geoff increasingly devoted himself to support and extend the burgeoning scientific field of his creation. The *Journal of the Autonomic Nervous System* (later *Autonomic Neuroscience: Basic and Clinical*) had been founded by Chandler McCluskey Brooks in 1978; from 1985 to 2016 Geoff was editor-in-chief. The journal *Purinergic Signalling* was founded by Geoff in 2004, and he was editor-in-chief until his death. It published a very wide range of articles covering signalling by purines in almost every organ



Figure 4. 'Lovers', one of Geoff's many wood carvings. Melbourne, about 1960. Credit: Burnstock family. (Online version in colour.)

system. Over the next 20 years, Geoff served on the editorial boards of more than 30 journals. He was the first president of the International Society for Autonomic Neuroscience, which has held large international meetings every two or three years since its founding in 1994. Through several visits to Chengdu, Geoff stimulated the interest of the acupuncture research community in possible purinergic mechanisms. He had indeed become the 'grand old man' of his field, encouraging the creation of purine clubs or societies in Italy, Germany, Japan, Brazil,



Figure 5. Burnstock family, (from left to right) Aviva, Tammy, Dina, Nomi and Geoff. Paraparaumu, New Zealand, 2019. Credit: Burnstock family. (Online version in colour.)

North America, the UK, Australia/New Zealand and China. Geoff always found the time to participate and engage, particularly with the younger attendees. Thus, his passion for science in general, and purines in particular, infected successive generations.

The clinical impact of Geoff's work increased markedly during this period. He collaborated extensively with clinicians, and he also advised Roche and later Afferent Pharmaceuticals (now acquired by Merck) in their efforts to develop a P2X3 receptor antagonist. This has now

paid off, with the launch of gefapixant for use in chronic cough—the first three letters of the name are a tribute to Geoff.

The most important drug that acts on P2Y receptors is clopidogrel, which was introduced into clinical practice in 1997. Its development largely resulted from the original observations of Gustav Born that ADP inhibits platelet aggregation (see Flower 2020). Clopidogrel irreversibly blocks a platelet P2Y receptor (P2Y12, formerly P2Y<sub>T</sub>). Drug development programmes continue with respect to several of the receptors, of which that for the P2X7 may be the most advanced. A small molecule activator of P2X7 receptors has been shown to sensitize non-small cell lung cancers in mice: the drug stimulates dendritic cells to secrete interleukin-18, which leads to production of interferon- $\gamma$  by T cells within the tumours (Douguet *et al.* 2021).

Geoff's enthusiastic popularization of the role of extracellular ATP went beyond the P2 receptors themselves. Monoclonal antibodies are important therapeutic options in oncology: such an antibody has recently been developed that binds only to its antigen in the presence of the high levels of extracellular ATP typically found in the tumour microenvironment, thus limiting 'off-target' side effects in normal tissues (Mimoto *et al.* 2020; Kamata-Sakurai *et al.* 2021).

Eventually, Geoff and Nomi moved from Hampstead to live in Melbourne once again. At the university there he continued to interact with young scientists through his appointments as honorary professor at the Department of Pharmacology and Therapeutics and honorary professorial fellow at the Florey Institute of Neuroscience and Mental Health.

## **PASSIONS AND INTERESTS**

Geoff in his younger years was passionate about boxing, which was a strong family tradition; he remained a fan of the sport. He introduced and championed table tennis at his school, and he played tennis himself for most of his life across the parkland from his home in Hampstead, London. His main passion and relaxation was wood-carving (figures 3 and 4), often starting with pieces collected on the beaches at Paraparaumu, New Zealand, where the Hirschfeld family had their beach house (figure 5). Even during their many years in the UK, Geoff and Nomi would spend some northern winter weeks at Paraparaumu.

Another of Geoff's favourite activities over many years was assembling jigsaw puzzles. Nomi was fond of describing his pastimes and achievements in verse, a well-known odyssey being entitled *That busy bee called ATP*. The final verse of her biographical *Geoff's story* provides a poetic epitaph:

He always had one on the go. And in New Zealand, the jig saw on the board simply works as metaphor for a life of striving, building, loving, dreaming, giving, learning and receiving.

#### Awards and honours

- 1970 Royal Society of Victoria Silver Medal
- 1971 Fellow of the Australian Academy of Science
- 1986 Fellow of the Royal Society
- 1987 Honorary Member of the Royal College of Physicians
- 1992 Member of Academia Europaea
- 1998 Fellow of the Academy of Medical Sciences
- 1998 Honorary Fellow of the Royal College of Surgeons of England
- 2000 Honorary Fellow of the Royal College of Physicians
- 2000 Royal Medal of the Royal Society of London
- 2002 Doctor Honoris Causa, University of Antwerp
- 2003 Correspondant Academicien of the Real Academia Nacional de Farmacia, Spain
- 2003 Honorary Member of the Physiological Society
- 2004 Honorary Fellow of the Pharmacological Society
- 2007 Doctor Honoris Causa, J. W. Goethe-Universität (Frankfurt)
- 2008 Honorary Member of the Australian Physiological Society
- 2009 Copernicus Gold Medal, Ferrara
- 2010 Gaddum Memorial Award, British Pharmacological Society
- 2011 Doctor Honoris Causa, University of Leipzig
- 2012 Erasmus Medal, Academia Europaea
- 2018 Macfarlane Burnet Medal, Australian Academy of Science
- 2018 Companion of the Order of Australia

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#### AUTHOR PROFILES

#### Richard Alan North



Alan North studied medicine and physiology at the University of Aberdeen. His PhD project in the group of Hans Kosterlitz in Aberdeen was to make intracellular recordings from neurons of the enteric nervous system, and to study the actions of opiates. This approach he then extended to many parts of the central nervous system, and to the discovery of ways in which neurotransmitters and drugs act on receptors to open and close ion channels in individual neurons. He held faculty positions in the USA at Loyola University of Chicago, the Massachusetts Institute of Technology and the Vollum

### **Biographical Memoirs**

Institute of Oregon Health Science University, and in the UK at the universities of Sheffield and Manchester. At the Glaxo Institute for Molecular Biology in Geneva, Alan led a group that isolated a cDNA for the P2X receptor, and subsequently determined molecular details of its operation as an ATP-gated ion channel. Alan is currently emeritus professor at the University of Manchester.

## Marcello Costa



Marcello Costa grew up in Argentina and Italy, and he completed his medical training in Torino in 1967. He was a lecturer at the University of Torino when he met Geoff Burnstock on the steps of a church in Venice in late 1969 at an international conference. A telegram followed, offering him a postdoctoral fellowship in Geoff's laboratory. Within months Marcello and his new wife were being welcomed not only in the Department of Zoology but also in Geoff's home. After Geoff's departure for the UK, Marcello was appointed as lecturer at Flinders University in Adelaide. Marcello pioneered the immunohistochemistry of the autonomic intestinal neurons, supplemented by electrophysiological and functional approaches; this

led to a better understanding of how the enteric nervous system controls gut movement and secretion. For near 20 years this was a collaboration with John Furness, then also at Flinders, who had met Marcello when working for his PhD in Geoff's laboratory. Marcello has been particularly active in the promotion of science-based medicine, and in the public understanding of neuroscience. He was a founder and later president of the Australian Neuroscience Society, and he is a Fellow of the Australian Academy of Science. In 2020 he was named an Officer of the Order of Australia. Marcello remains active in research as the Matthew Flinders Distinguished Professor at Flinders University.

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