

Geoffrey Burnstock 1929–2020[†]

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ABSTRACT

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 (NANC) 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 ten years later these categories were substantiated by cDNA cloning. From 1975 until his retirement in 1997, Geoff was head 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 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.

Keywords: ATP, biochemistry, physiology, protein-coupled, purinergic, transmission, zoology.

Early years and education

Geoffrey Burnstock (Fig. 1) was the 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 fourteen: he 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 had 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.

Published: 8 June 2022

Cite this:

North, R. A. and Costa, M. (2022)
Historical Records of Australian Science,
33(2), 160–171. doi:[10.1071/HR22004](https://doi.org/10.1071/HR22004)

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[†]This memoir was commissioned by *Biographical Memoirs of the Royal Society* and is published here with minor amendments. It was published by the Royal Society online on 18 August 2021 and is available at <https://doi.org/10.1098/rsbm.2021.0016>.

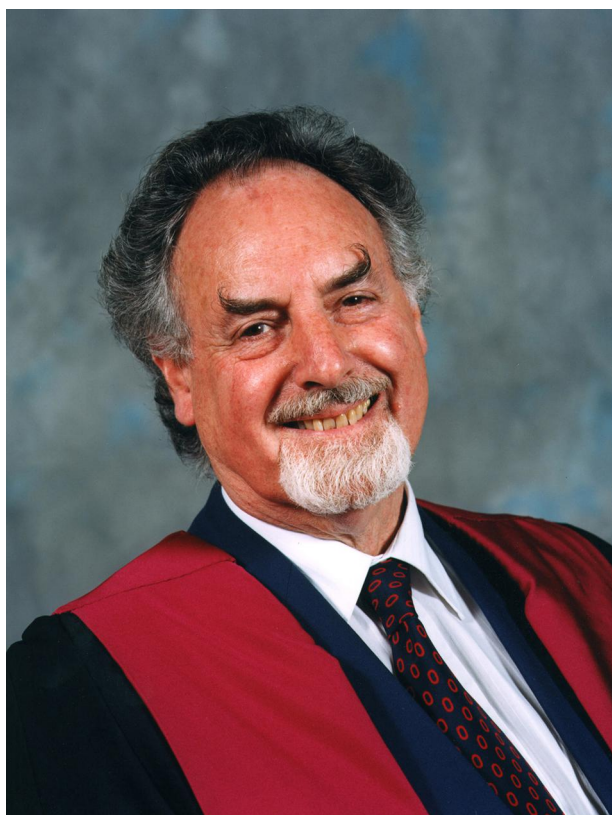


Fig. 1. Geoffrey Burnstock. Credit: Burnstock family.

Geoff applied to, but was rejected from, several medical schools because ‘I had the wrong accent, clothes and school background’.¹ 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), but with further A-levels in mathematics and physics he was again denied entry to medical school. His father died in 1948 and Geoff helped 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 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,² he later transferred to the supervision of J. Z. Young in the Department of Anatomy and Embryology at University College London (UCL). At KCL, he had initiated

discussion meetings at the interface of art, science, history and religion, together with contemporaries including Eric Barnard and Lewis Wolpert.

As he was finishing his PhD at UCL in 1957, Geoff met Nomi Hirschfeld, and they 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 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.³ Burnstock and Straub applied it to the taenia coli.⁴ 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 Bülbbring was the doyenne of smooth muscle physiology and, having seen Geoff’s technique, she invited him to join her group in Oxford. The young Australian Mollie Holman was then in Bülbbring’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.⁵ They also showed that acetylcholine depolarised and contracted the muscle,⁶ whereas noradrenaline hyperpolarised the membrane and inhibited spike activity.⁷

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 United States of America (USA), such as the Marine Biology Laboratory at Woods Hole, Massachusetts. While in the USA 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

¹Burnstock’s autobiography (Burnstock 2018) was a private publication, printed at Lavenham Press, Lavenham, Suffolk, UK.

²Burnstock (1957).

³Stämpfli (1954).

⁴Burnstock and Straub (1958).

⁵Bülbbring and others (1958)

⁶Burnstock (1958)

⁷Burnstock (1960).

class-conscious England and enjoy the positive Australian approach to new initiatives (“give-it-a-go-mate”).⁸

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. She 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 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 (Fig. 2).⁹ Mike Rand became Professor of Pharmacology at the University of Melbourne (in 1965) and remained a close colleague of Geoff's. Mollie Holman moved in 1963 to a senior lectureship in physiology at Monash University, which had just opened its doors to students in March 1961.

A critical period in the history of purinergic research, that 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: 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 hyperpolarisation was observed after a delay of about 200 ms: this



Fig. 2. Mollie Holman and Geoff Burnstock examining oscilloscope film, Melbourne, about 1960. Credit: Burnstock family.

was called an inhibitory junction potential (IJP) by analogy with the EJP seen in the vas deferens. The findings were communicated to the Australian 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*.¹⁰ This discovery was totally unexpected, and there was no mention of it in reviews by Burnstock and Holman¹¹ and by Burnstock, Holman and Prosser published earlier in 1963.¹² Paradoxically, as Graeme Campbell noted in his thoughtful recollections of these early times, Bülbring, Burnstock and Holman had already observed IJPs in their recordings from the taenia coli in Oxford, but without realising it.¹³

The next important steps in the characterisation 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 hyperpolarised stretched smooth muscle of the rabbit colon. But the IJP of the taenia coli was unaffected by drugs known to block noradrenergic transmission.¹⁴ In parallel, good evidence was provided that these non-cholinergic, non-adrenergic (NANC) neurones were also able actually to relax the intestinal smooth muscle.¹⁵ From then the hunt for the identity of the transmitter of the NANC inhibitory neurones 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

⁸Burnstock (2018).

⁹Burnstock and Holman (1960).

¹⁰Burnstock and others (1963c).

¹¹Burnstock and Holman (1963).

¹²Burnstock and others (1963a).

¹³Campbell (1970). Campbell (1991). Burnstock (1958).

¹⁴Burnstock and others (1963b). Burnstock and others (1964). Bennet and others (1966).

¹⁵Burnstock and others (1966).

possessed a rich NANC innervation, such as the stomach,¹⁶ had powerful relaxing effects on the taenia coli and that the most powerful component of these extracts was ATP.¹⁷ At that time, ATP was widely known as a carrier of energy within eukaryotic cells,¹⁸ but the further role of ATP in the phosphorylation of intracellular proteins such as enzymes, transporters and receptors, was barely recognised.¹⁹

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 1969,²⁰ and published in full in December 1970.²¹ Thus, the purinergic hypothesis of the NANC nerves was born.²²

Geoff maintained his strong and productive drive to prove the purinergic nature of the NANC inhibitory neurones 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 neurones 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 started his career.²³ 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 organisation filled with critical minds who, by and large, worked in parallel fields further away from the NANC neurones and retained a healthy skepticism 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 vertebrate and invertebrates (molluscs, fish, frogs, lizards, sheep, all small laboratory animals and of course



Fig. 3. On the boat returning from 'Hayman Island Smooth Muscle meeting', Barrier Reef, Queensland, September 1983. Credit: Alan North.

humans). He retained this active interest in smooth muscle and its innervation throughout his career (Fig. 3).

Return to University College London

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 the 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

¹⁶Campbell (1966). Campbell (1969).

¹⁷Campbell (1970).

¹⁸Kalckar (1941). Lipmann (1941).

¹⁹See, for example, Cohen (2002).

²⁰Burnstock and others (1969).

²¹Burnstock and others (1969).

²²Burnstock (1971). Burnstock (1972).

²³Burnstock (2018).

come from somewhere quite lacking 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.

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 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.²⁴

Geoff expanded the department greatly through the next two decades. He was recognised 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 inter-departmental collaboration and only very light touch direction from the faculty organisation. Geoff certainly treated the anatomy department as his fiefdom, and he was very effective in gaining support for it.²⁵

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 twenty-six full professors.

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

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 skilfully 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.²⁶

Co-transmission

Since the work of Otto Loewi and Sir Henry Dale, 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 branches of a single neurone would release the same chemical transmitter(s).²⁷ When it became clear from the work of Geoff's group in Melbourne that there was a non-adrenergic non-cholinergic (NANC) transmitter, the initial thinking was that there must be a third type of postganglionic nerve, that is, cholinergic,

²⁴Pers. comm. from John Parnavelas, with his permission to publish.

²⁵Pers. comm. to the authors from a person who prefers to remain anonymous.

²⁶Lieberman (1997).

²⁷Dale (1935).

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?' and reviewed the extensive evidence already available for co-existence of different putative transmitters in neurones.²⁸

Brownstein and his collaborators had shown biochemically the co-existence of several putative transmitters in a single *Aplysia* neurone,²⁹ the direct actions of peptides on mammalian neurones were beginning to come into focus (angiotensin,³⁰ substance P³¹). Immunohistochemical demonstrations of novel peptide-containing nerves were starting to show the widespread presence of peptides such as somatostatin and substance P in neurones of the gut³² and central nervous system.³³ 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 measuring the EJP, had concluded in 1960 that 'the transmitter was most likely to be noradrenaline'.³⁴ This conclusion was first called into question by Ambache and Aboozar, who measured the twitch response and used a range of catecholamine receptor antagonists.³⁵ It was known that ATP was released together with catecholamines from adrenal medullary vesicles,³⁶ and that ATP was co-stored with noradrenaline in vesicles from sympathetic nerves.³⁷ David Westfall's group in West Virginia showed that ATP or a related purine acted as a co-transmitter,³⁸ by measuring both the electrical and contractile response in the smooth muscle. Nerve stimulation evoked a biphasic contractile response, in which the fast component was blocked by $\alpha\beta$ meATP desensitisation 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 photo-activated ATP analog arylazidoaminopropionyl-ATP. The slower phase

was mimicked by noradrenaline and blocked by the $\alpha 1$ adrenoceptor 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 thereafter joined Geoff's laboratory at UCL and extended these observations to the rat tail artery and several other tissues.³⁹ 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 neurones, Geoff had shown in 1970 that ATP was the inhibitory transmitter released by non-adrenergic inhibitory nerves in the colon.⁴⁰ But he later found himself paradoxically on the defensive. Evidence began to accrue that NANC neurones in the taenia coli, which used ATP, also contained the vasoactive intestinal polypeptide (VIP).⁴¹ Functional studies showing that NANC inhibitory neurones in the gut utilised at least two different neurotransmitter mechanisms extended his very idea that neurons use more than one transmitter.⁴² With the discovery of nitric oxide (NO), a third substance present and involved in the transmission of the enteric NANC inhibitory neurones,⁴³ Geoff eventually accepted that the enteric purinergic neurones 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 and Szent-Györgyi, who had reported the effects of injection of adenylic acid in dogs and guinea pigs, with particular reference to effects on the heart.⁴⁴ Incidentally, that was also the year in which ATP itself was discovered by Subbarow and Fisk at Harvard,⁴⁵ and by Karl Lohmann in Otto Meyerhof's

²⁸Burnstock (1976).

²⁹Brownstein and others (1974).

³⁰Nicoll and Barker (1971).

³¹Konishi and Otsuka (1974).

³²Hökfelt and others (1975a).

³³Hökfelt and others (1975b).

³⁴Burnstock and Holman (1960).

³⁵Ambache and Aboozar (1971).

³⁶Carlsson and Hillarp (1956).

³⁷See for example Smith (1972).

³⁸Fedan and others (1981). Sneddon and others (1982).

³⁹Meldrum and Burnstock (1983). Sneddon and Burnstock (1984).

⁴⁰Burnstock and others (1970).

⁴¹Furness and others (1981).

⁴²Costa and others (1986).

⁴³Sanders and Ward (1992).

⁴⁴Drury and Szent-Györgyi (1929).

⁴⁵Fiske and Subbarow (1929).

laboratory in Berlin.⁴⁶ 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*.⁴⁷ The effects of extracellular adenosine 5'-diphosphate (ADP) were extensively studied with respect to platelet aggregation in the 1960s.⁴⁸ Gus Born 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 a 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,⁴⁹ but the first reference to a receptor for ATP (as distinct from adenosine, cAMP or ADP) was that of Bastien Gomperts.⁵⁰ He applied ATP (or ATP⁴⁻ as he would say, given that it was much more potent than MgATP) to permeabilise the membrane of mast cells, so that he could study the molecular machinery of histamine secretion.

Three methods have been used by pharmacologists to define receptors, before molecular and atomic structures were available. The first was by ranking the order of the potency of a series of structurally related agonists while measuring their effects in a range of different tissues: this was used to define α and β receptors for catecholamines such as adrenaline and noradrenaline.⁵¹ 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 (desensitisation). 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.⁵² 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.⁵³ 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 the adenosine, and they were not blocked by theophylline. In 1985, he further separated P2X and P2Y receptors (22).⁵⁴ The main distinguishing feature here was also the rank order of agonist potency: $\alpha\beta\text{meATP} > \beta\gamma\text{meATP} > \text{ATP} = 2\text{-methylthioATP}$ for P2X receptors, and the opposite for P2Y. But he also showed that $\alpha\beta\text{meATP}$ selectively desensitised P2X receptors. By this time, it was clear that ATP (and particularly $\alpha\beta\text{meATP}$) could directly activate ion channel receptors through P2X receptors,⁵⁵ whereas ATP (and particularly 2-methylthioATP) acted at P2Y receptors through intracellular G-proteins.⁵⁶ We now know that one downstream effect of transduction through G_{q/11} 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,⁵⁷ and G protein-coupled,⁵⁸ families were beginning to succumb to cDNA cloning in the mid-1980s. Although not skilled in molecular approaches, Geoff realised 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 that they collaborate to clone a P2 receptor cDNA.⁵⁹ Eric had been among the first to use the *Xenopus* oocytes to express cloned cDNAs, for nicotinic acetylcholine and γ -aminobutyric acid receptors.⁶⁰ In June 1993, they reported the cloning and expression of a P2Y receptor cDNA (P2Y1),⁶¹ at the same time as David Julius's group in San Francisco identified P2Y2.⁶² There are now eight of these (numbered 1, 2, 4, 6, 11, 12, 13 & 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),⁶³ and separately from the Julius laboratory (P2X2),⁶⁴ reported the cloning and

⁴⁶Lohmann (1929). The history of the discoveries has been recounted by Maruyama (1991).

⁴⁷Konijn and others (1967).

⁴⁸Gaarder and others (1961). Born (1962).

⁴⁹Reviewed by Flower (2020).

⁵⁰Cockcroft and Gomperts (1979). Cockcroft and Gomperts (1980). Bennett and others (1981). Gomperts (1983).

⁵¹Ahlquist (1948).

⁵²Schild (1947).

⁵³Burnstock (1978).

⁵⁴Burnstock and Kennedy (1985).

⁵⁵Krishtal and others (1983). Jahr and Jesell (1983). Kolb and Wakelam (1983).

⁵⁶Dubyak and De Young (1985).

⁵⁷Noda and others (1983).

⁵⁸Dixon and others (1986).

⁵⁹Barnard (2000).

⁶⁰Reviewed by Stephenson (2020).

⁶¹Webb and others (1993).

⁶²Lustig and others (1993).

⁶³Valera and others (1994).

⁶⁴Brake and others (1994).

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 and other colleagues at UCL to isolate further cDNA clones using homology-based approaches and these were published,⁶⁵ contemporaneously with reports from other laboratories.⁶⁶ There are now seven P2X receptor subunits, which form channels usually as homotrimers but sometimes as heterotrimers,⁶⁷ and eight members of the P2Y receptor family.⁶⁸ The receptor responsible for the permeabilisation 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 fifty a year, and indeed bore witness to his proselytising zeal.

Later years at the Royal Free

When Geoff Burnstock retired from the headship of the Department of Anatomy and Developmental Biology in 1997 (Fig. 4), 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 experimental work, while Geoff increasingly devoted himself to support and extending 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 system. Over the next twenty years, Geoff served on the editorial boards of more than thirty 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

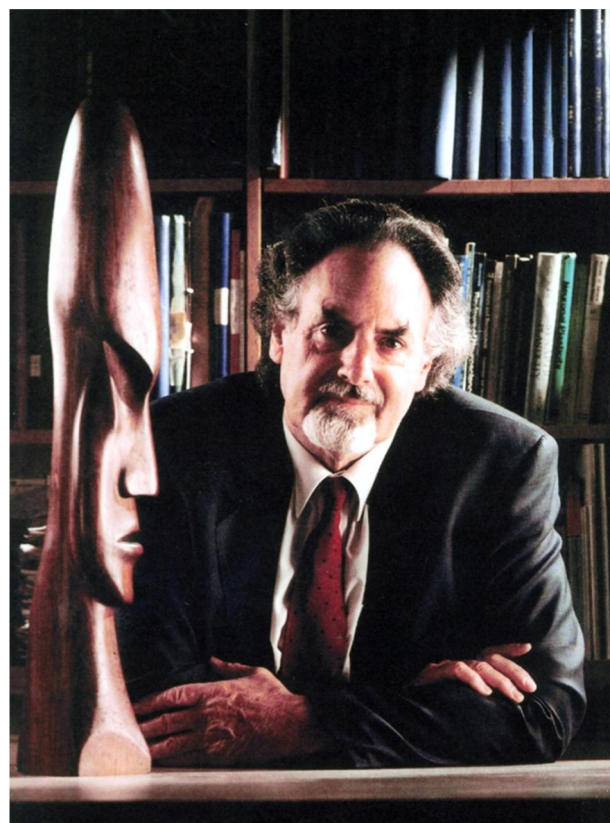


Fig. 4. In his office with wood sculpture, UCL, London, about 1997. Credit: Burnstock family.

the creation of purine clubs or societies in Italy, Germany, Japan, Brazil, North America, 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 Burnstock. The most important drug that acts on P2Y receptors is clopidogrel, which was already introduced into clinical practice in 1997. Its development largely resulted from the original observations of Gustav Born that ADP inhibits platelet aggregation.⁶⁹ Clopidogrel irreversibly blocks a platelet P2Y receptor (P2Y₁₂, formerly P2Y_T).

⁶⁵Chen and others (1995). Bo and others (1995).

⁶⁶Lewis and others (1995). Collo and others (1996).

⁶⁷Lewis and others (1995). North (2002).

⁶⁸Abbracchio and others (2006).

⁶⁹See Flower (2020).



Fig. 5. 'Lovers'—one of Geoff's many wood carvings. Melbourne, about 1960. Credit: Burnstock family.

Drug development programmes continue with respect to several of the receptors, of which the P2X7 may be the most advanced. A small molecule activator of P2X7 receptors has been shown to sensitise non-small cell lung cancers in mice: the drug stimulates dendritic cells to secrete interleukin-18, which leads to production of interferon- γ by T cells within the tumours.⁷⁰ Geoff's enthusiastic popularisation 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 which 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.⁷¹

Geoff officially retired from his position at the Royal Free and UCL in 2017 (when he was 88). He 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



Fig. 6. Burnstock family, (from left to right) Aviva, Tammy, Dina, Nomi and Geoff. Paraparaumu, New Zealand, 2019. Credit: Burnstock family.

at the Department of Pharmacology and Therapeutics, and honorary professorial fellow at the Florey Institute of Neuroscience and Mental Health.

Interests and passions

Geoff in his younger years was passionate about boxing, which was a strong family tradition, and 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. His main passion and relaxation was wood-carving (Figs 4, 5), often starting with pieces collected on the beaches at Paraparaumu, New Zealand where the Hirschfeld family had their beach house (Fig. 6). 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

⁷⁰Douguet and others (2021).

⁷¹Mimoto and others (2020). Kamata-Sakurai and others (2021).

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

Burnstock’s achievements were recognised in many ways, beginning in 1970 with the award of the Royal Society of Victoria silver medal, his election to fellowship of the Australian Academy of Science in 1971 and the Royal Society of London in 1986. He was awarded the Royal Medal of the Royal Society in 2000, and the Macfarlane Burnet Medal of the Australian Academy of Science in 2018. In 2018, he became Companion of the Order of Australia (AC). A full list of awards and honours, and a bibliography of his publications, is contained in the Supplementary Material to this biographical memoir.

Supplementary material

Supplementary material is available [online](#).

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Data availability. The authors assert that any data used in compilation of this biographical memoir is publicly accessible.

Conflicts of interest. The authors declare no conflicts of interest.

Declaration of funding. This research did not receive any specific funding.

Acknowledgements. We are grateful to David Attwell, Max Bennett, Ed Byrne, Tim Biscoe, Graeme Campbell, Francesco Di Virgilio, Giorgio Gabella, Malcolm Grant, Tomas Hökfelt, Charles Kennedy, Bob Lieberman, Elspeth McLachlan, John Parnavelas, Humphrey Rang, Derek Roberts, David Satchell, Peter Sneddon, Mike Spyer, John Wood and Clifford Woolf for sharing helpful recollections. We thank particularly Nomi Burnstock for her generous comments and provision of images. We are especially pleased with Geoff for writing an autobiography in 2018. This is entitled 'Against the odds' and printed by The Lavenham Press Ltd, Lavenham, Suffolk. The portrait photograph is from the Burnstock family collection. The copyright is unknown, but it was likely taken at UCL in around 2000.

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