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Burnstock G. Purinergic nerves. *Pharmacol. Rev.* 24:509-81, 1972.
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This review presented evidence supporting the existence of non-adrenergic, non-cholinergic autonomic nerves and the idea that intrinsic neurones supplying smooth muscle of the gut, bladder, and possibly other organs utilise a purine nucleotide, probably adenosine-5'-triphosphate, as the principal neurotransmitter. These neurones were termed "purinergic." The electrophysiology, pharmacology, neurochemistry, and structural basis of purinergic transmission were described. [The *SCI*® indicates that this paper has been cited in over 860 publications since 1972.]

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The story behind this paper really began in the early 1960s when, essentially by accident, two of my PhD students, Max Bennett and Graeme Campbell, and I uncovered clear evidence for the existence of non-adrenergic, non-cholinergic nerves. We were studying nerve transmission in the guinea pig taenia coli with the sucrose-gap technique. Both adrenergic and cholinergic nerve transmission had been blocked with guanethidine and atropine, so that we could observe the responses of the smooth muscle to direct stimulation. To our great surprise, we observed large transitory hyperpolarizations to single pulses, which led to cessation of spontaneous spike discharge and relaxation. The possibility that these responses were due to direct stimulation of muscle was excluded since they were abolished by tetrodotoxin, which blocks neuronal conduction but not action potentials in smooth muscle. They were thus established as inhibitory junction potentials (IJPs) resulting from stimulation of intramural non-adrenergic, non-cholinergic neurones.[1] Non-adrenergic, non-cholinergic nerves have since been found throughout the gastrointestinal tract of many vertebrate species as well as in parts of the urinogenital, respiratory, and cardiovascular systems.

Together with my colleagues, David Satchell, Campbell, Brian Dumsday, and Anne Smythe in Melbourne in the early 1970s,[2,3] and later with John Bevan and Che Su in California,[4] I carried out experiments to identify the transmitter in non-adrenergic, non-cholinergic nerves. Many substances were explored, but most were rejected because they were inactive or they did not mimic the nerve-mediated response or their action was due to stimulation of nerves and not to direct action on smooth muscle. A purine nucleotide, probably adenosine 5'-triphosphate (ATP), emerged as the most likely contender.[2,3] This finding was followed by a systematic series of experiments to investigate whether ATP satisfied the criteria generally regarded as necessary for establishing a substance as a neurotransmitter. On the basis of the evidence from these studies, in the 1972 article, I formulated the purinergic nerve hypothesis and coined the term "purinergic" for nerves utilising ATP as the principal transmitter, and proposed a model of the storage, release, and inactivation of ATP during purinergic transmission.

There may be several reasons that reference to this article continues to increase. First, the purinergic nerve hypothesis has been controversial. While evidence for purinergic innervation of some smooth muscles has been strengthened since 1972, it is recognised that other non-adrenergic, non-cholinergic nerves may utilise peptides, monoamines, or amino acids as neurotransmitters.[5] Second, the hypothesis has led to three important developments: (1) the establishment of ATP as a cotransmitter with noradrenaline in some sympathetic nerves and with acetylcholine in some cholinergic nerves and the discovery that adenosine, a breakdown product of ATP, acts as an inhibitor of the release of noradrenaline and acetylcholine;[6] (2) the proliferation of publications on purinergic receptors, triggered largely by the recognition of purinoceptor subtypes with selective agonists and antagonists and their wide distribution in central as well as peripheral systems;[7] and (3) the exploration of purinergic involvement in disease and its therapy.

1. **Bennett M R, Burnstock G & Holman M E.** Transmission from intramural inhibitory nerves to the smooth muscle of the guinea-pig taenia coli. *J. Physiol.—London* 182:541-58, 1966. (Cited 60 times.)
2. **Burnstock G, Campbell G, Satchell D G & Smythe A.** Evidence that adenosine triphosphate or a related nucleotide is the transmitter substance released by non-adrenergic inhibitory nerves in the gut. *Brit. J. Pharmacol.* 40:668-88, 1970. (Cited 285 times.)
3. **Burnstock G, Dumsday B H & Smythe A.** Atropine-resistant excitation of the urinary bladder: the possibility of transmission via nerves releasing a purine nucleotide. *Brit. J. Pharmacol.* 44:451-61, 1972. (Cited 130 times.)
4. **Su C, Bevan J A & Burnstock G.** (^{3}H) Adenosine triphosphate: release during stimulation of enteric nerves. *Science* 173:336-9, 1971. (Cited 60 times.)
5. **Burnstock G.** Neurotransmitters and trophic factors in the autonomic nervous system. (The Review Lecture.) *J. Physiol.—London* 313:1-35, 1981. (Cited 75 times.)
6. ----------, ed. *Purinergic receptors.* London: Chapman & Hall, 1981. 365 p. (Cited 35 times.)
7. ----------, Recent concepts of chemical communication between excitable cells. (Osborne N N, ed.) *Dale's principle and communication between neurones.* Oxford: Pergamon Press, 1983. p. 7-35.

