

This Week's Citation Classic

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Paton W D M. The action of morphine and related substances on contraction and on acetylcholine output of coaxially stimulated guinea-pig ileum.

Brit. J. Pharmacol. Chemother. 12:119-27, 1957.

[Department of Pharmacology, Royal College of Surgeons, London, England]

Morphine and other opiates were found to inhibit the twitches and acetylcholine output of the field-stimulated guinea-pig ileum preparation, in concentrations comparable to those required for clinical analgesia. [The *SCI*[†] indicates that this paper has been cited in over 800 publications.]

A "Paradigm of the Brain"

Sir William D.M. Paton
13 Staverton Road
Oxford OX2 6XH
England

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My research started with an invitation to a Gordon Conference in 1954 to talk on the autonomic pharmacology of the intestine. Although rather ignorant about this, I knew that a range of atropine-resistant phenomena had thrown serious doubt on cholinergic transmission in the gut. It seemed that the great need to clarify matters was for a nerve-effector preparation like those that taught us so much about neuromuscular and ganglionic synapses. But there was no simple "nerve" available, since the nerve network of the gut is embedded in its wall.

However, in the last century, Du Bois Raymond had shown that with a nerve placed not on electrodes but in a voltage *field*, stimulation would occur according to the component parallel to the nerve (the cosine law). So it occurred to me to try passing current between an electrode in the lumen of the intestine and one in the fluid outside, exposing the whole nerve network to an electric field, unchanged even if the gut moved. It worked admirably. The nerves could be selectively excited by short shocks, yielding beautifully regular twitch responses. This "nerve-muscle" preparation was then found, by all the classical cri-

teria, to be cholinergic. This work was left, for lack of time, as a brief report.¹ A later study with M. Aboo Zar using field stimulation of innervated and denervated ileum strips, made absolutely certain that the acetylcholine came from nervous tissue, and not (as had been suggested) partly from the muscle.²

Of the drugs active on gut to be analysed, morphine stood out as a puzzle. A clear answer was obtained: morphine and other opiates acted presynaptically, blocking release of the transmitter acetylcholine. The concentrations required were low and corresponded to those required for analgesia clinically. Tolerance phenomena occurred. The stimulated gut did indeed seem to offer a "paradigm of the brain."

The work has been significant in several ways. First, the stimulated ileum provides a simple but quantitative preparation for analysing cholinergic transmission. It makes an excellent class experiment in autonomic pharmacology.

Second, it has served as a sensitive and reproducible test for opiate action. It provided the first assay by which J. Hughes³ found evidence of the enkephalins. It played a similar role in identifying the endorphins. In establishing the existence of identifiable opiate receptors, the test enabled a wide correlation between opiate action and binding data.⁴

Third, the effectiveness of the technique prompted the widespread trial of field stimulation using other species and other structures where the nerves are embedded in the tissue, with considerable success.

Fourth, rather interestingly, it has provided a sensitive test for tetrahydrocannabinol action.

Finally, it has proved invaluable for industrial screening of morphine-like analgesics, by replacing the need to test drugs on the response of a conscious animal to pain. This is a significant contribution to animal welfare—a true "alternative method."⁵

1. Paton W D M. The response of the guinea-pig ileum to electrical stimulation by co-axial electrodes. *J. Physiology* 127:P40-P41, 1955. (Cited 90 times.)
2. Paton W D M & Zar M A. The origin of acetylcholine released from guineapig intestine and longitudinal muscle strips. *J. Physiology* 194:13-33, 1968. (Cited 520 times.)
3. Hughes J. Isolation of an endogenous compound from the brain with pharmacological properties similar to morphine. *Brain Res.* 88:295-308, 1975. (Cited 865 times.)
4. Pert C B & Snyder S H. Opiate receptor: demonstration in nervous tissue. *Science* 179:1011-4, 1973. (Cited 1,320 times.) [See also: Pert C B. The naloxone methodology and the discovery of opiate receptors. *Citation Classic, Current Contents Clinical Medicine* 17:40:16-7, 2 October 1989; *CC Life Sciences* 32:40:16-7, 2 October 1989; and *CC Social & Behavioral Sciences* 21:40:16-7, 2 October 1989.]
5. *Animal experiments and alternatives in biomedical research. European Research Councils report.* Strasbourg, 1989.

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