

# This Week's Citation Classic™

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**Gregory R A, Tracy H J, French J M & Sircus W.** Extraction of a gastrin-like substance from a pancreatic tumour in a case of Zollinger-Ellison syndrome. *Lancet* 1:1045-8, 1960.

[Dept. Physiology, Univ. Liverpool; Dept. Medicine, Univ. Birmingham, England; and Gastro-Intestinal Unit, Western General Hospital, Edinburgh, Scotland]

This paper established that the cause of the gastric hypersecretion in a case of the Zollinger-Ellison syndrome was the excessive and inappropriate secretion of a gastrin-like stimulant by a pancreatic tumour. [The SCJ® indicates that this paper has been cited in over 390 publications since 1960.]

R.A. Gregory  
Physiological Laboratory  
University of Liverpool  
Liverpool L69 3BX  
England

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Long before Zollinger and Ellison's<sup>1,2</sup> description of the condition with which their names were to be linked, clinicians had recognised and feared those rare cases of peptic ulcer characterised by severe acid hypersecretion, which would prove refractory to all treatment short of total gastrectomy and otherwise would probably end in death from perforations and haemorrhages. Zollinger and Ellison discovered a small pancreatic tumour in each of their two cases, and they made the seminal suggestion that the tumour might have caused the hypersecretion by producing a powerful secretagogue. However, their attempts to demonstrate such a substance in tumours obtained from subsequent cases were unsuccessful, and by 1960 it was widely doubted that there was any basis for their hypothesis. I met Zollinger in 1958 when I visited Columbus, Ohio, to lecture. The idea of a pancreatic stimulant of gastric secretion seemed unphysiological, and I was not greatly interested in the problem; little did I dream that 18 months later my partner Hilda Tracy and I would solve it!

How Tracy and I came to work on gastrin in 1959 has been recounted in a previous *Citation*

*Classic*.<sup>3</sup> By early 1960, we had a method of extracting the hormone from porcine gastric mucosa that provided a potent histamine-free product effective in conscious dogs and man. One day, a former pupil, Bill Sircus, of Edinburgh, wrote offering us a fragment of a pancreatic tumour removed from what must have been the first case of the Zollinger-Ellison (ZE) syndrome to be recognised as such in Britain. The patient had been relieved of his hypersecretion, jejunal ulceration, and diarrhoea. Most of the tumour had already been used in fruitless attempts to show that it contained a gastric secretagogue.

Tracy and I reasoned that if such tumours did produce a secretagogue, it must obviously survive passage through the liver and might therefore resemble gastrin. We decided to make a tumour extract by our method and test it on a conscious dog. When the tumour arrived, I was somewhat disappointed; it weighed less than one gram. Nevertheless, Tracy insisted we make the extract and test it. I left her to try it on one of our dogs while I went and did something that seemed more important. Fortunately, with her usual prudence, she first injected what I would have derided as an absurdly small portion of the extract—how wise she was! When I returned an hour or so later, the dog was happily impersonating a patient with ZE syndrome by giving a massive secretion of gastric acid. Tracy was taking blood samples that established that the response was not due to insulin hypoglycaemia.

With the remainder of the extract, we were able to confirm that the response did not depend upon innervation of the stomach and that the extract was free from histamine. Soon afterward, we and our colleagues showed that the metastases found in more than half of all ZE patients also produced the secretagogue,<sup>4</sup> which we eventually proved was human gastrin.<sup>5</sup>

Perhaps this paper has been frequently cited because it established the basis for the ZE syndrome and so contributed to the understanding and diagnosis of a life-threatening variety of peptic ulcer, now recognized to be more common in a comparatively mild form than was originally realised.<sup>6</sup>

1. Zollinger R M & Ellison E. Primary peptic ulcerations of the jejunum associated with islet cell tumors of the pancreas. *Ann. Surg.* 142:709-28, 1955. [See also: Zollinger R M. *Citation Classic. Current Contents/Clinical Practice* 8(4):14, 28 January 1980.]
2. Zollinger R M & Coleman D W. *The influences of pancreatic tumors on the stomach.* Springfield, IL: Thomas, 1974. 205 p. (Cited 10 times.)
3. Gregory R A. *Citation Classic. Commentary on Gut* 5:103-17, 1964. *Current Contents/Life Sciences* 26(45):23, 7 November 1983.
4. Grossman M I, Tracy H J & Gregory R A. Zollinger-Ellison syndrome in a Bantu woman, with isolation of a gastrin-like substance from the primary and secondary tumors. II. Extraction of gastrin-like activity from tumors. *Gastroenterology* 41:87-91, 1961. (Cited 95 times.)
5. Gregory R A, Tracy H J, Agarwal K L & Grossman M I. Aminoacid constitution of two gastrins isolated from Zollinger-Ellison tumour tissue. *Gut* 10:t003-8, 1969. (Cited 60 times.)
6. McGuigan J E. Islet cell tumors and the ulcerogenic syndrome. *Monographs Pathol.* 21:177-84, 1980.