

Gregory R A & Tracy H J. Isolation of two "big gastrins" from Zollinger-Ellison tumour tissue. *Lancet* 2:797-9, 1972.
[Physiological Laboratory, University of Liverpool, England]

A pair of larger gastrin peptides embodying the heptadecapeptide amides ("little gastrins") previously described by the same authors were isolated from Zollinger-Ellison tumor tissue. They corresponded in chromatographic and electrophoretic properties to the "big gastrins" identified immunologically in hypergastrinaemic sera. Later work substantiated the surmise that though both were potent stimulants of gastric acid secretion they constituted a precursor form, or progastrin. [The *SCI*® indicates that this paper has been cited in over 205 publications.]

Horriying the Safety Officer

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Reading again the little paper that is the subject of this *Citation Classic* reminded us of the vast increase in methodological resources for the isolation and characterisation of peptide hormones that has occurred since H.J. Tracy and I did the work. We had earlier isolated gastrin from gastric antral mucosa and had discovered that it was the powerful gastric secretagogue inappropriately produced by the pancreatic and other tumors found in cases of the Zollinger-Ellison (ZE) syndrome, a condition of severe peptic ulceration due to gastric acid hypersecretion.¹ From 1968 we were aware that in our antral extracts a very small proportion of the bioactivity present was in molecules considerably larger than the heptadecapeptide amides (G17) we and our chemist colleagues in Liverpool led by George Kenner had identified as the major form. We knew that small amounts of G17 might bind to denatured protein and so present the appearance of a large molecular form, but we nevertheless thought it worthwhile to attempt to isolate the big component in our extracts in case it should prove to be a genuine precursor. Isolation of the big gastrins was not easy; they were difficult to separate from the G17s by chromatography and we had to set up column electrophoresis in a volatile buffer. As the paper shows, it did

the trick and we used it with great success and no little pride, until the University Safety Officer saw it and was horrified at our disregard of the possible hazards!

A far more promising starting material would have been ZE tumor tissue, which is usually very rich in gastrin, but, until we had mastered the problems of isolating the porcine big gastrins, we dared not try our hand with the small amount of tumor we possessed. After our successful extraction in 1960 of gastrin from a ZE pancreatic tumor, people in many countries sent us tumors to extract and test, because this provided a certain diagnosis in a suspected case of the syndrome and at that time the only effective treatment was total gastrectomy. After 1972 diagnosis and treatment was transformed by the general availability of gastrin radioimmunoassay and H₂ blockers, but, during the 10 years for which we provided this service to clinicians, we were able to accumulate some active tumor tissue. We first used some to isolate the G17s and prove their identity with the human antral forms; then, as this paper mentions, we committed four years' collection to isolation of the big gastrins.

Meanwhile, R.S. Yalow and S.A. Berson had applied their epoch-making method of radioimmunoassay to the analysis of serum gastrin.² By gel filtration and electrophoresis, they showed in hypergastrinemic serum a major component ("big gastrin," BG) larger than G17 ("little gastrin," LG). On brief trypsin digestion of the serum, BG disappeared and LG increased. Their hypothesis that by analogy with the enzymatic conversion of proinsulin to insulin BG might consist of LG extended N-terminally through a pair of basic amino acid residues was substantiated by the work described in this paper, which is perhaps why it has often been quoted in association with theirs. It was Louis Dancsi, a Hungarian biochemist working with George Kenner, who skillfully digested our pure BGs with trypsin, separated the several products by high-voltage paper electrophoresis, characterised them by quantitative amino acid analysis, and even provided us with samples to test for bioactivity! Although the general structure of BG and its relation to LG was thus established, the full sequencing of porcine and human forms and their total synthesis took several years to accomplish. Sad to say, two who played leading roles in this later phase—leuan Harris of Cambridge, England, and Kenner—did not live to see the successful conclusion of their work and confirmation of the precursor status of BG by complete sequencing of the gastrin gene, achieved in Chicago by Kan Agarwal, a former member of Kenner's team in Liverpool.³

1. Gregory R A. The gastrointestinal hormones: a review of recent advances. The Bayliss-Starling Lecture 1973. *J. Physiology* 241:1-32, 1974. (Cited 90 times.)
2. Yalow R S & Berson S A. Further studies on the nature of immunoreactive gastrin in human plasma. *Gastroenterology* 60:203-14, 1971. (Cited 160 times.)
3. Gregory R A. Gastrin. *Advan. Metab. Disord.* 11:163-98, 1988.

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