

This Week's Citation Classic

Williams E D, Karim S M M & Sandler M. Prostaglandin secretion by medullary carcinoma of the thyroid: a possible cause of the associated diarrhoea. *Lancet* 1:22-3, 1968. [Dept. Pathol., Royal Postgrad. Med. Sch.; Inst. Obstet. and Gynaecol. and Bernhard Baron Mem. Res. Labs., Queen Charlotte's Maternity Hosp., London, England]

Significant levels of prostaglandins E₂ and F_{2a} were found in medullary carcinoma extracts, and peripheral and tumour venous blood, but not in appropriate controls. Tumour produced prostaglandins, possibly in concert with other agents, may play a role in production of the tumour associated diarrhoea. [The SCI® indicates that this paper has been cited over 310 times since 1968.]

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July 22, 1981

"The request to write one's own history of some of one's own work seems too flattering to resist—I wonder how many refuse? In my case, the invitation came as a double surprise—that I should be asked at all, and that the article quoted should be the one it was.

"In 1963, I realised that medullary carcinoma of the thyroid was likely to be a tumour of C cells, and that C cells were the likely source of the recently discovered hormone, calcitonin. I therefore began a retrospective study of patients with medullary carcinoma to look for evidence of the effects of excess calcitonin production, starting with the obvious and rather naive idea that hypocalcaemia was the most likely. The cases were collected by reclassifying the pathology of several hundred cases of thyroid carcinoma from four different London hospitals. Disappointingly, hypocalcaemia only occurred following thyroparathyroidectomy, but, surprisingly, many patients had unexplained diarrhoea. A humoral link seemed possible, particularly as diarrhoea was more common in patients with wide-

spread tumour, remitting in some after tumour removal only to recur with tumour spread. A paper describing these findings was, after earlier rejection, published,¹ and was quickly confirmed.

"The watery diarrhoea was accompanied by very rapid small intestinal transit, and I showed *in vitro* that tumour extracts stimulated intestinal muscle contraction. As activity was destroyed by proteolysis, I became interested in the possibility that prostaglandins, then recently recognised as of potential clinical importance, were involved. Sultan Karim and Merton Sandier took over the assay work, and found prostaglandins E₂ and F_{2a} in tumour extracts and tumour venous effluent obtained at operation; we speculated that prostaglandin production might cause the diarrhoea.

"The work has been frequently quoted as the first report of prostaglandin production by tumours, the first to attribute a syndrome to this production, and the first reasonable explanation of the diarrhoea associated with medullary carcinoma of the thyroid. In the intervening 13 years, prostaglandin production by medullary carcinoma has been substantiated;² the cause of the diarrhoea remains uncertain.

"Medullary carcinoma is now known to produce many other substances, including somatostatin, serotonin, histaminase, nerve growth factor, ACTH, CRH, VIP, carcinoembryonic antigen, and substance P.³ Substance P and VIP affect smallgut motility and secretion; calcitonin itself increases jejunal water and salt secretion.⁴ Prostaglandins, calcitonin, serotonin, and substance P and VIP may therefore all play a role in the diarrhoea associated with medullary carcinoma. The fact that one tumour produces such a variety of substances with a converging effect should stimulate further thought—after all, the differentiation of an endocrine cell can be regarded as directed towards a functional effect rather than hormone structure. It would be interesting, if improbable, if my next article in *Current Contents®* could start, 'The idea came to me while I was writing my last *Citation Classic... V*' "

1. Williams E D. Diarrhoea and thyroid carcinoma. *Proc. Roy. Soc. Med.* 59:602-3, 1966.
2. Barrowman J A, Bennett A, Hillenbrand P, Rolles K, Pollock D J & Wright J T. Diarrhoea in thyroid medullary carcinoma: role of prostaglandins and therapeutic effect of nutmeg. *Brit. Med. J.* 3:11-12, 1975.
3. Williams E D. Medullary carcinoma of the thyroid. (DeGroot L J. ed.) *Endocrinology* New York: Grune & Stratton. 1979. Vol. 2. p. 777-92.
4. Kennedy Gray T, Bleberdori F A & Fordtrran J S. Thyrocalcitonin and the jejunal absorption of calcium, water, and electrolytes in normal subjects. *J Clin Invest* 52:3084-8, 1973