CC/NUMBER 19
MAY 10, 1982

This Week's Citation Classic

Pearse A G E. The cytochemistry and ultrastructure of polypeptide hormone-producing cells of the APUD series and the embryologic, physiologic and pathologic implications of the concept. *J. Histochem. Cytochem.* 17:303-13, 1969. [Royal Postgraduate Medical School, London, England]

This paper is essentially the distillation of some four years of work on the common cytochemical and ultrastructural characteristics of a widespread and otherwise apparently unconnected collection of endocrine and presumed endocrine cells. Their most convincing marker characteristic gave rise to the acronym APUD, by which the whole series came ultimately to be recognized. [The *SCI*® indicates that this paper has been cited over 805 times since 1969.]

Anthony G.E. Pearse
Royal Postgraduate Medical School
University of London
London W12 0HS
England

January 11, 1982

"This paper was first presented at the Third International Congress of Histochemistry and Cytochemistry, held in New York in August 1968. It doubtlessly became the most cited of my contemporary papers because it was the first full and public expression of the APUD concept. Its content has remained valid, subject to minor modifications, up to the present time.

"Acquisition of the mass of facts leading up to the definitive formulation of the concept, and its feeding into my internal computer, had occupied 15 years of wide ranging cytochemical and ultrastructural studies. But one afternoon, late in 1964, I was examining under the microscope a series of dog thyroid preparations from which I hoped to derive information on the functional characteristics of the parafollicular cells. The latter had earlier in the year been identified as the source of Harold Copp's new hormone, calcitonin.[1,2] For the first and only time in my life I was able to cry εὕρηκα, for the parafollicular cells had all the cytochemical characteristics of those known endocrine cells, in the pituitary, pancreas, adrenals, and stomach, on which I had spent so many years of enquiry. Two years later, I had acquired sufficient courage to propound the concept[3,4] and a further two elapsed before the acronym APUD (*not* Anthony Pearse's Ultimate Dogma, but Amine Precursor Uptake and Decarboxylation) appeared in print.[5]

"In these three papers a significant collective declaration was made that the APUD cells were derived from precursors of 'neural origin, perhaps coming from the neural crest.' For some of the cells, by then 40 in number, this proved to be the case but when studies by several groups of workers[6-8] showed that the 18 gastroenteropancreatic (GEP) APUD cells were not neural crest derivatives, the concept was modified to permit their origin from 'neuroendocrine programmed epiblast.'

"Marker studies[3-5,9,10] have now established with virtual certainty the neuroectodermal origin of all the APUD cells, GEP and non-GEP alike. They thus take their rightful place as constituents of the third, and oldest, division of the nervous system.[11]

"Recognition of the validity of the concept in some quarters has antedated its general acceptance. Perhaps because the diffuse neuroendocrine system is an acknowledged successor to the earlier 'diffuse endokrine epitheliale Organe' of the Austrian pathologist Friedrich von Feyrter (1895-1973),[12] election to membership of the Deutsche Akademie der Naturforscher Leopoldina (1973) and to the Deutsche Gesellschaft für Endokrinologie (1978) were followed by the award of the Ernst Jung Prize for Medicine (1979). The second Fred W. Stewart Prize, awarded to me in that same year by the Memorial Sloan-Kettering Cancer Center, New York, was clearly due to the vested interest of that establishment in oncology, and hence in my work on the neuroendocrine tumors (apudomas), while the clear acceptance of these as a real entity by the surgical fraternity led to the award of the 1976-1978 Triennial John Hunter Prize of the Royal College of Surgeons of England. But better than prizes is the knowledge that my intuitively derived views, expressed in the cited publication, have withstood the collective efforts of a dedicated band of falsifiers. To them, for their stimulating opposition, and to those who have supported me, I am equally grateful."

1. **Copp D H, Cameron E C, Cheney B A, Davidson A G F & Henze K G.** Evidence for calcitonin—a new hormone from the parathyroid that lowers blood calcium. *Endocrinology* 70:638-49, 1962.
2. **Foster G V, McIntyre I & Pearse A G E.** Calcitonin production and the mitochondrion-rich cells of the dog thyroid. *Nature* 203:1029-30, 1964.
3. **Pearse A G E.** 5-Hydroxytryptophan uptake by dog thyroid C cells and its possible significance in polypeptide hormone production. *Nature* 211:598-600, 1966.
4. **----------.** Common cytochemical properties of cells producing polypeptide hormones, with particular reference to calcitonin and the C cells. *Vet. Rec.* 79:587-90, 1966.
5. **----------.** Common cytochemical characteristics of cells producing polypeptide hormones (the APUD series) and their relevance to thyroid and ultimobranchial C cells and calcitonin. *Proc. Roy. Soc. B* 170:71-80, 1968.
6. **Le Douarin N & Teillet M A.** The migration of neural crest cells to the wall of the digestive tract in the avian embryo. *J. Embryol. Exp. Morphol.* 30:31-48, 1973.
7. **Andrew A.** Further evidence that enterochromaffin cells are not derived from the neural crest. *J. Embryol. Exp. Morphol.* 31:589-98, 1974.
8. **Pictet R L, Rall L B, Phelps P & Rutter W J.** The neural crest and the origins of the insulin-producing and other gastrointestinal hormone-producing cells. *Science* 191:191-2, 1976.
9. **Teitelman G, Joh T H & Reis D J.** Transformation of catecholaminergic precursors into glucagon (A) cells in mouse embryo pancreas. *Proc. Nat. Acad. Sci. US* 78:5225-9, 1981.
10. **Schmechel D, Marangos P J & Brightman M.** Neurone-specific enolase is a molecular marker for peripheral and central neuroendocrine cells. *Nature* 276:834-6, 1978.
11. **Pearse A G E.** Islet cell precursors are neurones. *Nature* 295:96-7, 1982.
12. **von Feyrter F.** *Über diffuse endokrine epitheliale Organe.* Leipzig: J.A. Barth, 1938. 62 p.