This Week's Citation Classic


This paper is essentially the distillation of some four years of work on the common cytochemical and structural characteristics of dispersed endocrine cells, all of which were referred to as APUD cells, by which the whole series came ultimately to be recognized. [The SC® indicates that this paper has been cited over 805 times since 1969.]

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"This paper was first presented at the Third International Congress of Histochemistry and Cytochemistry, held in New York in August 1968. It doubtlessly became one of the most cited 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 acceptance into my 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 'Eureka!', for the parafollicular cells had all the cytochemical characteristics of those known endocrine cells, the pituitary, pancreas, adrenals, and stomach, on which I had spent so many years of inquiry. Two years later, I had acquired sufficient courage to propound the concept3,4 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 'nerve 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 workers6-8 showed that the 18 gastroenteropancreatic (GEP) APUD cells were not nerve crest derivatives, the concept was modified to permit their origin from 'neuroendocrine programmed epithelium.'

"Marker studies9,10 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 endocrine epithelium 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 esteemed interest of that establishment in oncology, and hence in my work on the neuroendocrine tumors (apudomas), while the collection 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 devised 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."