THE DISPERSED NEUROENDOCRINE SYSTEM AND ITS COMPONENTS IN THE BRONCHIAL TREE

It is safe to state that during the last 2 decades numerous factual observations and conceptual developments have led to a remarkable growth in traditional endocrinology whose breadth and significance have increased considerably. In this regard, the development of the APUD (Amine Precursor Uptake and Decarboxylation) concept and its eventual evolution into that of the DNS (Dispersed Neuroendocrine System) concept have played key roles. These developments have been facilitated by the increasingly widespread application of refined techniques such as electron microscopy, immunohistochemistry, tissue culture, etc. Information has accumulated and continues to accumulate very rapidly. It is therefore particularly useful to pause occasionally, to summarize and reiterate a few notions and conclusions that, currently at least, appear to be solidly established:

1) that similar or even identical biogenic amines and peptide hormones (*common peptides*) can be found in true central nervous system neurons, in peripheral nerves, in endocrine organs such as the hypophysis, in clusters of endocrine cells such as pancreatic islets and pulmonary neuroepithelial bodies (NEB's), and in a *system* of widely scattered cells (DNS) present in numerous tissues and organs including the gastrointestinal and bronchopulmonary tracts, the skin, etc.

2) that biogenic amines are not the monopoly of true neurons and neuron-like cells. And neither are peptide hormones exclusive of true endocrine cells given the evidence that neurons can produce them, store them, and use them as neurotransmitters. Thus, the concept of *peptidergic neurons* has arisen.

3) that peptides and classical neurotransmitters can coexist in single neurons, in single neuron-like cells (paraganglia) as well as in single, true endocrine cells.

4) that the entire organism is controlled and regulated by a single though not simple system of chemical messengers consisting of closely related biogenic amines and peptides which can act not only as neurotransmitters and true hormones but also as paracrine regulators of numerous cell functions including modulation of growth and development.

The majority of the aforementioned ideas have been developed on studies performed on the central nervous system and the gastrointestinal tract; however, they retain their basic validity and may, to a considerable extent, be transferred to other organ systems such as the bronchopulmonary tract. In this context, the lung has recently emerged as having an anatomically and functionally highly significant complement of endocrine cells.

Not surprisingly, many of these concepts have already had a remarkable impact upon diagnostic pathology and clinical medicine. In this brief editorial, data pertinent to the bronchopulmonary tract will be outlined.

The DNS components of the bronchopulmonary tract include the solitary neuroendocrine (NE) cells and the neuroepithelial bodies (NEB's). By electron microscopy both components display the characteristic membrane bound neurosecretory granules; however, structurally, the granule population appears heterogeneous which suggest that more than one material is being produced. Immunohistochemical analyses have indeed confirmed this suspicion Solitary bronchial NE cells have been shown to contain bombesin, calcitonin, leu-enkephalin and serotonin while NEB's display a similar complement except for the apparent absence of leu-enkephalin. Predictably, both NE cells and NEB's contain NSE (neuron specific enolase).

The functional role of and possible interplay between bronchial solitary NE cells and NEB's are not entirely clear. Yet, current ideas are to the effect that NEB's may function as intrapulmonary chemoreceptors responsive to hypoxia and hypercapnia whereas solitary NE cells may possess an essentially local-paracrine-regulatory role.

There is little question that neuroendocrine cells of the bronchopulmonary tract play an important role in the pathobiology of the said tract. Experimental studies have shown that the administration of substances such as nitroso compounds (particularly diethylnitrosamine or DEN) to hamsters result in an apparently selective proliferation of NEB's. These hyperplastic NEB's express a hormonal complement similar to that of their normal counterparts; however, when NEB cells from DEN-treated hamsters are cultured *in vitro*,a considerable proportion of the resulting cells express ACTH. This provocative observation would indicate that certain microenvironmental changes may result in the expression of a hormone which is *ectopic* for the lung.

Studies by several groups carried out on human pulmonary specimens with various types of chronic injury such as bronchiectasis and fibrosis have revealed a distinct hyperplasia of bronchial solitary NE cells and NEB's. Not surprisingly, many associated *tumorlets* and a few *microcarcinoids* were found in such specimens. These hyperplastic NE cells and NEB's tend to express the same materials as the normal components; however, in frankly dysplastic foci, *ectopic* meterials may be identified including ACTH, somatostatin and VIP (vasoactive intestinal polypeptide). Hyperplastic NE cells and NEB's have also been found in high altitude populations (3800-4300 meters) suggesting indeed an adaptive response to the *natural*, environmental chronic hypoxia.

Bronchopulmonary neoplasms of neuroendocrine differentiation may be considered to constitute a spectrum in which 4 distinct types are included. These are morphologically identifiable and carry considerable clinical and prognostic implications:

1) *true-typical-carcinoids*. These tumors are very predominantly central in location.Histologically, they are very well differentiated in spite of frequent invasion of the surrounding structures; mitoses are very rare. Distant metastases are uncommon and occur late in the course of the disease. Hormones expressed tend to parallel the normal complement although extopic meterials may be readily found. Clinical syndromes are rare. Ultrastructurally, the cells tend to be richly granulated.

2) *well differentiated neuroendocrine carcinomas*; these tumors are often referred to as *atypical* or *malignant* carcinoids; some cases have been misinterpreted as *early* small cell carcinomas. This type is predominantly peripheral; in our experience more than one third presents with metastases, and more than 50% develop metastases within 5 years. Histologically, they are atypical and mitoses are readily found. Ectopic hormones such as ACTH are readily demonstrated, and clinically evident hormonal syndromes are not rare. Ultrastructurally these tumors show granules readily, but less frequently than true carcinoids.

3) *nuroendocrine carcinomas of intermediate cell type*; these neoplasms show a vague *organoid* pattern and are comprised of polygonal to fusiform cells with notable peripheral palisading. Pleomorphism is marked and mitoses are frequent. The clinical course is aggressive, and metastases are the rule. Eutopic and ectopic hormones as well as NSE are readily expressed, and clinical syndromes can be present. Ultrastructurally, neurosecretory granules are scanty.

4) *neuroendocrine carcinomas of small cell type*; these are the well known and clinically aggressive *oat* cell carcinomas. Again, eutopic as well as ectopic materials may be found while by electron microscopy, neurosecretory granules are scanty.

Mixed forms of intermediate and small cell carcinoma may be found. More notable, is that some long term survivors of small and intermediate cell neuroendocrine carcinomas may die with widespread metastases which however display squamous or glandular features. These and related observations have suggested the notion of the *interconvertibility* of these tumors and the curently favored idea that all of them may arise from a common precursor or stem cell.

This necessarily brief and contracted outline indicates that neuroendocrine neoplasms of the lung as well as the hyperplasias and dysplasias that may be either associated with them or occasionally precede them,may express a broad spectrum of immunoreactive hormones and other materials such as NSE. Synchronous or asynchronous expression of multiple meterials is frequent. There is considerable evidence that these materials — and possibly their metabolites — may also be detected and measured in tumor tissue as well as in body fluids. Therefore, their potential use as clinical and pathologic *tumor markers* becomes evident. These notions are no longer of merely academic interest for it may be predicted that some of them and new ones not yet developed, will become rapidly incorporated into our diagnostic armamentarium. Some of these tests are already *routinely* performed in a number of laboratories our own included. These observations are also of evident clinical significance with regard to prognosis and therapy. This process will doubtless continue; the future appears bright and promising.

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