

## Plurihormonal Pituitary Tumors: Beyond The One Cell–One Hormone Theory

For most of this century, normal and neoplastic cells of adenohypophyseal origin were the subject of an elementary philosophy that relegated these cellular elements to the seemingly predictable, dedicated, and regimented function of specifically producing a single hormonal product. Liberated from the conceptual banalities and physiological inaccuracies of this now obsolete *one cell–one hormone* theory, these and other cells of endocrine origin have begun to declare unexpected aspects of their functionality, vis à vis their intriguing capacity to simultaneously produce multiple hormonal products. Designated as plurihormonality, this multihormone processing capability was once considered a rare and anomalous phenomenon of endocrine pathology. However, more than a decade of detailed immunohistochemical, ultrastructural, and biochemical appraisal has confirmed the contrary, for plurihormonality has emerged with sufficient regularity in normal and neoplastic endocrine states that it challenges some of the most fundamental concepts of cytogenesis and functional organization of the normal and neoplastic adenohypophysis. Existing and regimented paradigms of cellular differentiation, plasticity, structure–function correlates, and tumorigenesis in the pituitary may require some reconsideration in view of the broadened functional capabilities exhibited by these plurihormonal cells. Beyond the mere academic and taxonomic considerations, plurihormonality may also be of practical significance, as its occurrence in pituitary adenomas appears to adversely affect their biology and clinical course. Therefore, the problem of plurihormonality is of both clinical and conceptual consequence, and the following comments attempt to address these and related issues in consort.

In considering plurihormonality, one is immediately faced with the dilemma that this is a phenomenon without consensus definition. In that significant latitude exists

in the interpretation of the word “plurihormonal,” the translation of this term into a practical and universally accepted context has proved difficult. On the one extreme, plurihormonal can be used to denote the endocrinological phenomenon occurring in vivo, as demonstrated by elevations of multiple hormones in the blood of patients with pituitary tumors. On the other extreme, plurihormonal can also refer to the phenomenon of hormone release in vitro, in which tumor cells are observed to release multiple hormones when studied with the sequential reverse hemolytic plaque assay. Alternatively, plurihormonal can be used in a purely morphological context, reflecting the tumor’s hormonal content, and defined by the immunoreactive presence of multiple hormonal products within the tumor cell(s). Finally, and most recently, plurihormonal has been considered at a molecular level and can represent the expression of messenger RNAs for multiple hormones, as determined by in situ hybridization and Northern analysis. Because the in vivo, in vitro, immunohistochemical, and molecular definitions of plurihormonal do not always concur, issuing a precise definition has been problematic. Although each of these methodologies has specific merits and limitations, we feel that the term plurihormonal is conceptually and consistently most informative when used to describe the immunohistochemical profile of the tumor. Therefore, plurihormonality is defined here as immunopositivity for two or more functionally unrelated hormonal products within the same tumor cell. The definition has been broadened to also include tumors composed of multiple (bi- and trimorphous) cell populations, each engaged in the production of a different hormonal product. Although individual cells of such tumors may not be truly plurihormonal in isolation, the tumor is as a whole legitimized as plurihormonal, given its chimeric constitution.

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Insofar as the literature on plurihormonality has been both restricted to and polarized by anecdotal case reports and small isolated series, reliable estimates of the precise incidence of plurihormonal tumors awaits definitive confirmation. In one of the few surveys dedicated exclusively to the study of plurihormonality, Scheithauer et al. suggested that plurihormonal tumors account for up to 15% of all pituitary neoplasms [3]. Furthermore, plurihormonality appeared with unexpected regularity in pediatric pituitary tumors and in pituitary tumors associated with the MEN I syndrome.

In contrast to the many conceptual obscurities surrounding the problem of plurihormonality, the pathology of plurihormonal pituitary tumors is comparatively well established. Ushered in by the discovery of the first bihormonal tumors more than a decade ago, a diverse pathological spectrum of plurihormonal entities has since emerged, both in terms of morphological complexity and hormone expression. Given that there are seven potential secretory products expressed by pituitary tumors (GH, PRL, ACTH, LH, FSH, TSH, and alpha-subunit), the potential combinations of different hormones both in number and in kind are theoretically numerous. In practice, however, there appears to be some predictability to the general pattern of hormone expression among these plurihormonal entities, although unusual combinations may also occur. First, plurihormonal tumors occur most commonly in the clinical setting of acromegaly, where they constitute approximately 50% of all tumors producing the acromegalic state [1]. These tumors most commonly coexpress GH and PRL. Other common combinations include GH, alpha-subunit, and/or TSH; and GH, PRL, and alpha-subunit and/or TSH. The other common class of plurihormonal tumors are those composed of cells resembling glycoprotein hormone producing cells, and express any combination of LH/FSH, TSH, GH, and occasionally PRL. Rarely these tumors are associated with a hypersecretory state, presenting instead as a nonfunctioning sellar mass. Less intuitive combinations such as those coexpressing ACTH

with other hormonal products may also occur, but are distinctly uncommon.

Electron microscopy has been of paramount importance in deciphering the multiple immunoreactivities observed in plurihormonal tumors and precisely defining their morphological constitution. As mentioned, plurihormonal tumors can assume a variety of morphological configurations, ranging from a uniform monomorphous cell population wherein every cell is capable of generating multiple hormonal products, to a plurimorphous chimeric tumor in which each of several discrete cell populations is dedicated to the production of a single hormonal product. The potential fluidity of cell differentiation and the concept of transdifferentiation implicate a complex relationship between these "discrete" cell populations

Perhaps the most compelling motivation for understanding plurihormonality pertains to suspicions that plurihormonal pituitary tumors may be more aggressive than their monohormonal counterparts. The concept is not without precedence, for plurihormonality in other endocrine neoplasms (pancreatic endocrine tumors, medullary carcinoma of the thyroid) has been thought to portend a more malignant clinical course than that of monohormonal counterparts [2]. Evidence in support of a similar phenomenon in the pituitary is gaining strength, but more data are needed. It is known that the overwhelming majority of plurihormonal pituitary adenomas are macroadenomas at presentation, even in the presence of a hypersecretory syndrome [4]. Furthermore, more than 50% of all plurihormonal tumors are locally invasive at the time of diagnosis [3].

Although the epidemiological, morphological, and prognostic data provide some superficial insight into the nature of plurihormonal adenomas, these observations alone furnish little understanding of the biology of these tumors. These observations must somehow be integrated to explain plurihormonal tumor cytogenesis. We have become comfortable enough with the satisfying correlations that exist between the cytoarchitecture, hormonal content, and secretory function of the monohormonal pituitary tumors to generally accept

that pituitary tumors arise as well-differentiated monoclonal expansions of cellular elements normally present in the pituitary. Therefore pituitary tumors are accepted to have arisen from either normal somatotrophs, lactotrophs, corticotrophs, thyrotrophs, or gonadotrophs, and despite the multistep nature of tumorigenesis, the resultant tumors tend to maintain the structural and functional characteristics of the cell of origin. So convincing have been these unidirectional lineage patterns of neoplastic differentiation, that they form the basis for contemporary diagnosis, nomenclature, and classification of pituitary tumors. With the increasing recognition of plurihormonal tumors it has become distressingly clear that our regimented perspectives of pituitary tumorigenesis and cytogenesis may not be as unifying and all inclusive as once thought. One hypothesis is that plurihormonal adenomas arise in progenitor cells which can undergo multidirectional differentiation, generating a tumor capable of producing multiple hormonal products. This is an appealing prospect, especially for the complex monomorphous plurihormonal tumors. Alternatively, some plurihormonal tumors may arise in mature plurihormonal clones normally present in the pituitary; in the course of neoplastic transformation, these cells could remain monomorphous and plurihormonal or could transdifferentiate to produce a chimeric tumor composed of multiple populations of different hormone-producing cells. Pivotal to both these hypotheses is the conclusive demonstration of a plurihormonal progenitor cell within the normal nontumorous pituitary. We have on occasion identified cells expressing GH and TSH (somatothyrotrophs) and, more frequently, cells expressing GH and PRL (mammosomatotrophs) in the nontumorous pituitary [2]. Further study will be necessary to determine the extent to which the diverse plurihormonal expression identified in pituitary tumors is correspondingly

represented in cells of the nontumorous pituitary.

Having emerged to relinquish definitively any lingering ties to the one cell—one hormone theory, plurihormonal pituitary tumors have forced us to reevaluate the functional capabilities of the normal and neoplastic adenohypophyseal cell. They have given us some indirect insight into the functional plasticity of pituitary cells, which may be essential to understanding what takes place in the pituitary during fetal development, during certain periods of health such as pregnancy, and in certain nonneoplastic disease such as target organ endocrine failure. Only by reconciling the many unanswered questions accompanying the phenomenon of plurihormonality can we begin to appreciate fully what lies beyond the one cell—one hormone theory.

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