Cytogenesis of Nonfunctioning Pituitary Adenomas

Approximately 30% of surgically removed pituitary adenomas are unaccompanied by clinical and biochemical evidence of hormone excess [4, 11, 14], with the exception of mild hyperprolactinemia, which may occur in some patients, particularly in those harboring large tumors. The elevation of serum prolactin levels is explained by the so-called stalk section effect [18]; it is claimed that the growing tumor compresses or impairs the hypothalamus or the hypophyseal stalk, thereby suppressing the synthesis, release, or adeno-hypophyseal transport of dopamine, the main hypothalamic factor inhibiting prolactin discharge [18]. Nonfunctioning pituitary tumors are discovered either incidentally at autopsy or by various imaging techniques during the patient's life or because of local symptoms, such as visual disturbances, various cranial nerve palsies, headache, nausea, increased intracranial pressure, or various degrees of hypopituitarism [9, 11].

Some of these tumors are diffusely immunoreactive for one or more adeno-hypophyseal hormones as assessed by immunocytochemistry, and their cellular composition can be revealed by electron-microscopical investigation. These neoplasms, termed *silent pituitary adenomas*, consist of corticotrophs, somatotrophs, or other cell types; may express growth hormone, prolactin, or adreno-corticotrophic hormone genes; and comprise the minority of clinically and biochemically nonfunctioning pituitary tumors [7, 16, 17]. Lesions other than pituitary adenomas may also be found in the surgically removed tissues of patients in whom a nonfunctioning pituitary adenoma has been diagnosed. Various neoplasms, such as craniopharyngioma, meningioma, metastatic carcinoma, and plasmacytoma, and nonneoplastic lesions, such as lymphocytic hypophysitis and thyrotroph hyperplasia, have been documented [13]. These findings underline the importance of careful morphological studies in patients having a nonfunctioning pituitary tumor.

The substantial majority of nonfunctioning pituitary tumors consists of cells lacking specific markers of the established adeno-hy-

pophyseal cell types, and their morphological features are not indicative of differentiation along any one adeno-hypophyseal cell line [4, 11, 14]. By electron microscopy, the cells of these adenomas invariably show the presence of secretory granules and contain cytoplasmic organelles required for hormone synthesis and release. The endocrine function and cytogenesis of these adenomas are, however, unclear. Lack of knowledge regarding their cellular derivation is reflected in the confusion about terminology. Various terms, such as *fetal*, *embryonal*, *chromophobic*, *nonfunctioning*, *nonsecreting*, *undifferentiated*, and *precursor cell adenomas* were used to classify these lesions into distinct entities. However, none of these terms expresses their true nature or provides clues to their cytogenesis. In 1980, the term *null cell adenoma of the pituitary* was introduced to create interest in these obscure neoplasms [15]. The name *null cell adenoma* was borrowed from immunology (B, T, and null lymphocytes) to stress the most conspicuous feature of these tumors: the absence of specific markers that would permit the disclosure of their cytogenesis.

During the last decade, Snyder [19] and his group contributed significantly to the understanding of nonfunctioning pituitary adenomas. They deserve credit not only for calling attention to these intriguing neoplasms but also for emphasizing the close association between this group of tumors and gonadotroph adenomas. In a recent paper, they postulated that many nonfunctioning pituitary adenomas arise in gonadotrophs [3]. This suggestion is of considerable importance because of implications regarding pathogenesis, biological behavior, growth rate, recurrence, and treatment.

The question of cytogenesis is obviously a major challenge to those who study the pathology of pituitary tumors. There is no doubt that a large majority of clinically nonfunctioning pituitary adenomas is capable of synthesizing follicle-stimulating hormone (FSH), luteinizing hormone (LH), and alpha-subunit. They show focal immunoreactivity for these hormones [11] and release them

in vitro, as demonstrated by radioimmunoassay [1] and the reverse hemolytic plaque assay [20]. Stimulation with gonadotropin-releasing hormone or thyrotropin-releasing hormone often increases gonadotropin discharge in vivo and in vitro [2]. It was also revealed that 79% of clinically nonfunctioning pituitary adenomas contain messenger RNA for pituitary glycoprotein hormones [8].

We are uncertain, however, whether the available evidence is sufficiently strong to prove that most nonfunctioning pituitary adenomas originate in mature gonadotrophs. Cell derivation cannot be clarified without morphological studies. The use of sophisticated morphological techniques has advanced our understanding of pituitary adenoma cytogenesis. Investigations utilizing transmission electron microscopy have indicated that only a few clinically nonfunctioning adenomas are composed of well-differentiated gonadotrophs [11, 14]. In many cases, gonadotroph adenoma cells differ in histological and electron-microscopical characteristics from those of nontumorous gonadotrophs [5, 12]. It was also shown that gonadotroph adenomas in women have distinct ultrastructural differences from those in men [6]. This sexual dimorphism is unique in human tumors and can be so striking that the gender of the patient can be established by studying the electron-microscopical features of the tumor.

Although some clinically and biochemically nonfunctioning pituitary adenomas may, indeed, originate in mature gonadotrophs, we wish to propose an alternative hypothesis. In our view, the majority of clinically and biochemically nonfunctioning pituitary adenomas arise in uncommitted or committed precursor cells that can undergo differentiation toward various cell lines, most often to cells that produce FSH, LH, and alpha-subunit. This concept is supported by a recent case that clearly showed multidirectional differentiation of endocrinologically inactive null cells into well-granulated growth hormone-, prolactin-, thyroid-stimulating hormone-, and alpha-subunit-producing cells [10]. Since the publication of this case, we have seen several similar tumors. One might ask what mechanism is responsible for the neoplastic transformation of the mature gonadotroph. However, we believe the focus

should be on the investigation of potential precursor cells, to establish their existence, determine their characteristics, and identify the factors underlying their neoplastic transformation and proliferation. One might then ask why neoplastic transformation occurs mainly in older individuals, why oncocyctic change is frequent in these tumors and, most importantly, what factors account for the differentiation of a hormonally inactive precursor cell to a cell producing mainly FSH, LH, and alpha-subunit. Pathology is changing: Is it not more exciting to study in which direction a cell is going than to ask from where it is coming?

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