INTRODUCTION
A large number of morphological studies have been carried out on human pituitary adenomas over the last two decades primarily in order to establish structure-function correlations so as to provide the clinical endocrinologist with information of diagnostic interest on the endocrine activity of tumors. Classifications were made, based on the morphological observations, supporting and integrating those based on clinical manifestations and blood hormone concentration measurements.

Great advances in morphological diagnosis and classification have been made, mainly in the eighties, due to the considerable improvement in the morphological procedures. However the first approach, made by means of the histological staining methods, was far from adequate. Pituitary adenomas were divided into acidophilic, basophilic and chromophobic tumors according to the staining affinities of the cell cytoplasm. However, the tinctorial characteristics of the cells proved to give a poor indication of the type of their endocrine activity. This classification, therefore, has no diagnostic value (1, 2).

Electron microscopic studies gave more insights into structure and activity of the tumor cells. The peculiarities of the cellular organelles were accurately considered. Thus, the development of the rough endoplasmic reticulum and the prominence of Golgi complex (the cytoplasmic organelles responsible for the synthesis and packaging of the hormones) typical of many adenocarcinoma cells were related to their high secretory activity. Number, size and cellular location of secretory granules were found to differ according to the type of hormone stored within them. These observations allowed a classification of the tumors to be made according to the hormones produced, as inferred from the ultrastructural features of the cellular organelles, mainly of the secretory granules (1, 3-5). However the electron microscopy only provided indirect and subjective criteria to recognize the different types of tumors.

The turning point in the morphological studies of pituitary adenomas was the advent of the immunohistochemical techniques (immunofluorescence and immunoperoxidase methods). By using specific antisera it was possible to identify directly the hormones stored within the cells. The application of these techniques led to a much more precise and reliable distinction of the different tumor types. Since the mid-seventies a large number of papers reporting immunohistochemical studies on pituitary adenomas have been published (for books and comprehensive articles see Refs. 6-16).

The large scale immunohistochemical testing of adenomas for all known pituitary hormones as well as the improvement in the techniques made it increasingly evident that adenomas producing more than one hormone were much more common than could be deduced from blood hormone measurements and clinical symptoms. In addition, the deeper insight into hormonal content of adenomas gained by these techniques led to the finding that many “non-functioning” adenomas contained one or more pituitary hormones even though their presence did not result in an increase in their blood concentrations. All these findings were confirmed and stressed when highly sensitive immunoelectron microscopic techniques became available. Particularly the protein A-gold immunotechnique has been demonstrated over the last few years to be an extraordi-
narily useful tool to detect very low amounts of hormones stored within a cell.
The availability of advanced morphological procedures has also recently led to a series of extremely interesting findings often of great interest also to biologists. By the application of the protein-A gold double labelling technique the presence in many tumors of cells containing more than one hormone has been definitely ascertained. These mixed cells, observed at the same time also in normal pituitaries, are regarded as one of the more interesting new findings concerning the pituitary gland biology of the last few years. The availability of specific antibodies has also enabled researchers to demonstrate the presence in adenoma cells of a number of substances other than the known pituitary hormones. Some of them are at present considered of potential interest as diagnostic markers. Finally, morphological investigations have proved to be useful for shedding light on the mechanisms of action of drugs used in the management of pituitary tumors. These interesting findings which have emerged in recent years will be dealt with in this article, which will therefore comprise the following sections: 1) New insights into the hormonal content of pituitary tumors. The plurihormonal adenomas. The non-functioning adenomas; 2) The mixed cells; 3) Cellular products other than the known pituitary hormones. The diagnostic markers; 4) Effects of drugs on the ultrastructure of adenoma cells. The interested reader can find comprehensive and systematic depictions of all morphological features of the different types of human pituitary adenomas in a number of pertinent articles listed in the bibliography (2, 17-20).

**NEW INSIGHTS INTO THE HORMONAL CONTENT OF PITUITARY TUMORS. THE PLURIHORMONAL ADENOMAS. THE NON-FUNCTIONING ADENOMAS**

With the exception of GH- and PRL-secreting adenomas, tumors producing two or more hormones were considered quite rare. This idea was due to the fact that hormones present in the cells without concomitant increases in their serum levels went unnoticed. Early histochemical and immunohistochemical studies also suggested that most pituitary adenomas were composed of almost homogeneous cell populations engaged in the production of a single hormone (with the obvious exception of the non-functioning tumors apparently deprived of endocrine activity) (6, 21). The improvement in morphological techniques and the systematic search for all known pituitary hormones have proved it to be otherwise and have led to the increasing recognition of adenomas with plurihormonal immunohistochemical patterns, which however in most cases did not result in raised circulating levels of all hormones present in the cells (19-22). It is predictable that the frequency of plurihormonal adenomas will rise still more in the future if the protein A-gold immunoelectron microscopic technique is applied on larger scale.

The most common form of plurihormonal adenoma produces GH and PRL (9, 14, 20, 23-38). As mentioned above the existence of this kind of tumor was early recognized since in many cases both hormones were hypersecreted and patients had acromegaly and hyperprolactinemia. Immunohistochemical and immunoelectron microscopic studies have demonstrated that also tumors removed from patients presenting only with acromegaly or hyperprolactinemia contain both hormones (9, 14, 27, 29, 31, 32, 35, 37, 38). A recent classification indicates that the frequency of GH- and PRL-producing adenomas in unselected surgical material from more than one thousand tumors was 8-9%, which corresponded to about one-third of the total amount of tumors producing GH or GH/PRL (20). However, in recent studies using the protein A-gold technique 50% of tumors from acromegalic patients with or without hyperprolactinemia were found to contain GH and PRL immunoreactivities (35). This result suggests that the frequency of this tumor could be notably higher than that calculated using less sensitive techniques. It is reasonable to think that the association of normal hormonal levels with positive immunostaining is due to the fact that hormones are secreted in amounts insufficient to bring about detectable increases in their blood concentrations. This in turn can be due to a small number of cells engaged in the production of the hormones or to a low rate release. In keeping with the former explanation a positive correlation has been found between the basal PRL levels of acromegalic patients and the percentage of PRL positive cells in the tumors. Under 20-25% PRL positive cells the patients had no hyperprolactinemia (35).

Less usual hormonal associations have also been found in pituitary adenomas by immunohistochemistry, mainly in recent years. A broad spectrum of combinations of all pituitary hormones has been