Pathological Study of Carcinoid Tumors

Thesis

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By

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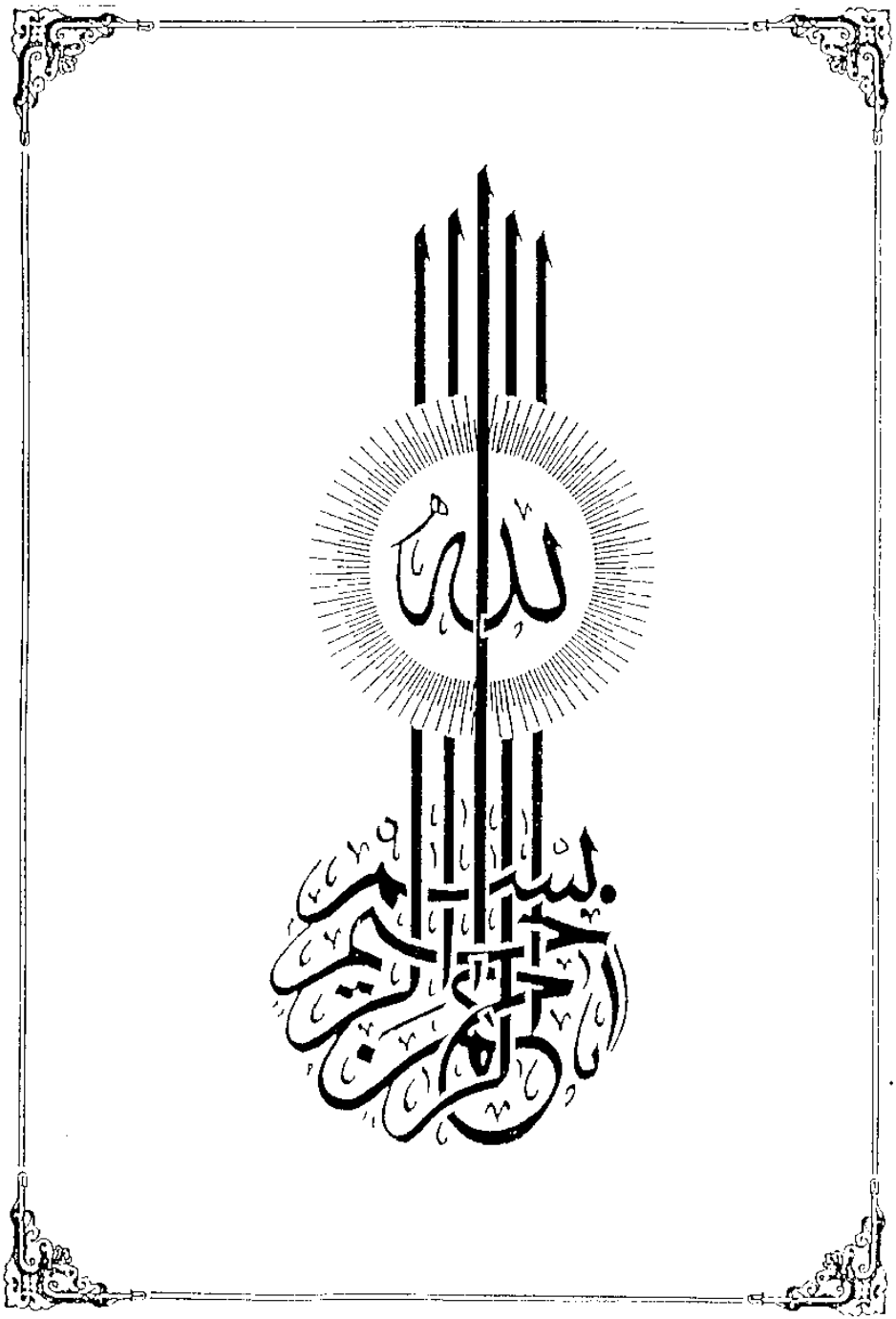
To
My Father, My Mother
&
My Husband



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Introduction & Aim of the Work

INTRODUCTION AND AIM OF THE WORK

Carcinoid tumors are derived from cells that were originally described by *Kulchitsky (1897)*, more recently they have been called enterochromaffin or enterochromaffin like cells *(Zeitels et al., 1982)*. These cells exhibit amine precursor uptake and decarboxylase (APUD) characteristics, hence, carcinoid tumors are apudomas *(Pearse and Polak, 1971)*.

Carcinoid tumors have attracted particular interest in the last two decades. Although they were originally considered to be benign, it is now recognized that extra-appendiceal carcinoids are frequently malignant. Carcinoids are found in the gastrointestinal tract, biliary tract, ovary and lung. In the small intestine and appendix they are the most common tumors *(Cheek and Wilson, 1970)*

Carcinoid tumors continue to be interesting and important for two very different reasons. First, they are part of the amine precursor uptake, decarboxylase (APUD) system. As such they secrete diverse amines and polypeptide hormones that result in unique and complex clinical pictures, the carcinoid syndrome. Second, both the site of origin and the malignant potential of these tumors are highly variable. *(Zeitels et al., 1982)*

Therefore, the aim of the present work is to describe the gross and microscopic appearances of carcinoid tumors in different sites. Any significant relation to age or sex will be included.

Review of Literature

REVIEW OF LITERATURE

HISTOLOGY

History of Argentaffin Cells

Argentaffin cells were first described by *Heidenhain* in *1870*, however, the credit for their discovery had generally been assigned to Kulchitsky, and hence, they were often referred to as Kulchitsky cells. In *1906, Ciacco* called them enterochromaffin cells because of an apparent similarity to the chromaffin cells of the adrenal medulla. *(Weichert, 1970).*

Feyrter (1951, 1954 and 1958) thoroughly studied the distribution of the argentaffin cells. He described them in the alimentary mucosa from the mouth to the anus, and were most common in the appendix, terminal ileum, duodenum and Meckel's diverticulum. Also he described them in other derivatives of the primitive gut, namely, the salivary glands, nasal mucosa, bronchi, biliary and pancreatic ducts, gall bladder and genitourinary system.

Feyrter (1969) considered these cells in the gastrointestinal tract to be peripheral endocrine or paracrine cells.

APUD Concept

Pearse (1969) postulated that a group of apparently unrelated endocrine cells, some in endocrine glands, others in non endocrine tissues, show a number of cytochemical and ultrastructural characteristics. These characteristics, from the initial letters of four of which the term

APUD is derived, indicate the possession of a common metabolic pattern and common synthetic storage and secretion mechanisms.

He also listed the cells included within the APUD series:

1. Pituitary corticotroph.
2. Pituitary melanotroph.
3. Pancreatic islet B cells.
4. Pancreatic islet α_2 cell.
5. Thyroid and extrathyroid C. cell.
6. Stomach - enterochromaffin cell (Gastrin, secretin).
7. Intestine - enterochromaffin cell (secretin, glucagon, CCK-P_3).
8. Pancreatic islet α cells.
9. Carotid body type I cell.
10. Lung endocrine cell.
11. Adrenal medulla A cell.
12. Adrenal medulla NA cell.

Origin of the APUD Cell

Pearse and Polak (1971) mentioned that APUD cells are derived from the neural crest, but they could not determine whether all the endocrine polypeptide cells of the adult gastrointestinal tract and pancreas are descendants of neural crest APUD cells or whether, some are derived by differentiation from the epithelial cells of the gut.

However, *Andrews (1976)* doubted about the neural crest origin of neurosecretory cells, and suggested that cells that have a similar biologic function may not reflect a common embryologic derivation, so he

postulated that stem cells from any of the three embryologic layers can diverge to neurosecretory differentiation.

Also, *Le Douarin (1978)* showed by detailed embryologic studies that APUD cells are of endodermal derivation.

Recently, *Dayal and Delellis (1989)* suggested that the term APUD is no longer in vogue, and the peptide and amine producing cells of the gut and other cells are called neuroendocrine cells.

Characteristics of APUD Cells

Pearse (1969) described the cytochemical characteristics of polypeptide hormone secreting cells of the APUD series.

(A) 1. Fluorogenic amine content (catecholamine, 5 HT or other)
   a) Primary b) Secondary uptake

(P)

(U) 2. Amine precursor uptake (5 HTP, DOPA)

(D) 3. Amino acid decarboxylase

4. High side chain carboxyl or carboxyamide (masked metrachromasia).
5. High non-specific estrase or choline estrase or both.
6. High α G P D (α glycerophosphate menadione reductase).
7. Specific immunofluorescence.

He also described the ultrastructural characteristics of polypeptide secreting APUD cells.

1. Low levels of rough (granular) endoplasmic reticulum.
2. High levels of smooth endoplasmic reticulum as vesicles.

3. Electron dense, fixation labile mitochondria.
4. Prominent microtubules, centrosomes.
5. High content of free ribosomes.
6. Tendency to produce fine protein microfibrils (especially when neoplastic).
7. Membrane bound secretion vesicles, best preserved by glutaraldehyde, varying density; average size 100-200 mu.

Description of Cells in the Gastrointestinal Tract

(Bloom and Fawcett, 1986)

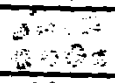
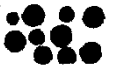
Enteroendocrine cells are described as small, granulated cells that are widely scattered throughout the epithelial lining of the gastrointestinal tract. They are present in moderate numbers in stomach, are common in the duodenum, more sparse in the jejunum and ileum where they occur both in the villi and in the crypts, and are also found in the biliary tract and the ducts of the pancreas.

At the light microscopic level, they are ovoid or pyramidal in the stomach and intestinal crypts, and more columnar on the epithelium of the villi. The bulk of the cell body is in the lower half of the epithelium, but a narrow apical region usually extends to the lumen, and has a brush border. The nucleus is rounded and generally poor in heterochromatin, the cytoplasm is pale in relation to the surrounding cells, the secretory granules vary in size in the different cell types and concentrate in the basal cytoplasm.

By Electron Microscopic Studies

The microvilli are often longer and thicker than those of adjacent absorptive cells, a finding that suggests their function as chemoreceptors, the cytoplasm is relatively electron lucent, the cytoplasmic organelles don't differ significantly in size or form from other epithelial cells.

Morphological differentiation between the various types depends on size, shape, electron density of secretory granules, complemented by immunocytochemical staining of granules with fluorescein labelled antibodies specific for their amine or polypeptide products, 16 types of cells are described and shown in the following table.

CELL TYPE	SECRETION GRANULES	LOCALIZATION Pancreas	Stomach	Intestines	PRODUCT
A	 250 nm	Islets			Glucagon, Glicentin
B	 350	Islets			Insulin
D	 350	Islets	Fundic Pyloric	Jejunum Ileum Colon	Somatostatin
D_1	 160	Islets	Fundic Pyloric	Jejunum Ileum Colon	Unknown
EC	 300	Islets	Fundic Pyloric	Jejunum Ileum Colon	Serotonin Various peptides
ECL	 450		Fundic		Histamine
G	 300		Pyloric	Duodenum	Gastrin
I	 250			Jejunum Ileum	Cholecystokinin
K	 350			Jejunum Ileum	Gastric inhibitory peptide
L	 400			Jejunum Ileum Colon	Glucagon-like immunoreactivity
Mo				Jejunum Ileum	Motilin
N	 300			Ileum	Neurotensin
P	 120		Fundic Pyloric	Jejunum	Unknown
PP	 180	Islets	Fundic Pyloric	Colon	Pancreatic polypeptide
S	 200			Jejunum Ileum	Secretin
TG				Jejunum	C-terminal gastrin immunoreactivity
X	 300		Fundic Pyloric		Unknown

Summary of the enteroendocrine cell types thus far described, including their nomenclature, their distribution, the ultrastructure of their granules, and their amine or peptide products. (Modified after Grube, H., and G. Forssmann, Horm. Metab. Res. 11: 603, 1979).

In the Lungs

Gosney et al. (1988) studied the distribution of neuroendocrine cells. They extend from the trachea to the alveolar ducts, but none are seen in the alveoli. 72% are present in the bronchi, 24% in the bronchioles (almost entirely in terminal rather than respiratory bronchioles) and only 4% in alveolar ducts. They are either solitary or form clusters, the solitary cells are pyramidal or columnar in shape and basally located in the epithelium of the airways. The clusters which were also described by *Frolich (1949)* contain four to eight cells each in the plane of section passing through them. They can be called neuroepithelial bodies if innervated as suggested by *Lauweryns and Peuskens (1972).*

The pulmonary neuroendocrine cells are thought to contain some peptides among which is 5 hydroxytryptamine *(Lauweryns et al., 1973),* gastrin releasing peptide *(Wharton et al., 1978),* calcitonin *(Becker et al., 1980)* and leucine enkephalin *(Cutz et al., 1981).*