APUDOMA

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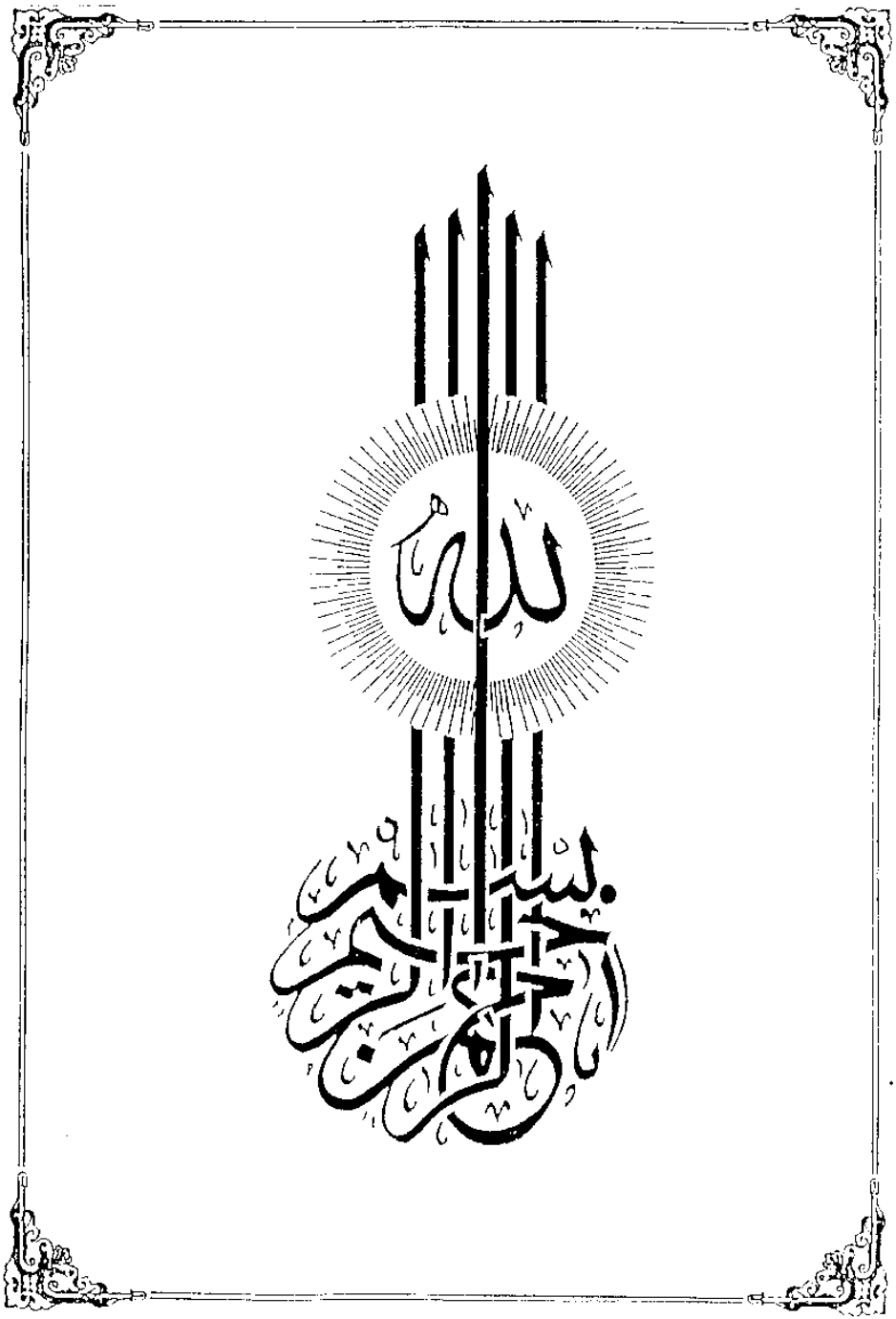

TO THE MEMMORY OF MY LATE NOBILE MOTHER

TO MY FATHER

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By definition Apudomas are tumours arising from APUD system. APUD system is related to a population of neuro endocrine cells named APUD cells. APUD is an acronym taken from the initial letters of most common cytochemical characteristics of these cells. These cells are capable of amine precursor uptake and decarboxylation, So A letter refers to their contents of amines (catecholamines & serotonin); PU to potential of preferential up take amines precursors (Dopamine and 5-hydroxy tryptamine) and D to amino acid decarboxylase enzyme which is responsible for decarboxylation reaction. **(Pearse; 1973).**

Apudomas are classified according to their specific peptides or amines into three types. Frist; orthoendocrine Apudomas which secrete excessively their normal products of polypeptides or amines as polypeptides of pituitary (adenoma), thyroid (medullary thyroid carcinoma) or pancreatic islet cells (insulinoma , glucagonoma and gastrinoma) or amines of adrenal medullary cells (pheochromocytoma) or kultschitzky cells of intestine (carcinoid). Secend; paraendocrine Apudomas which secrete products that normaly are not produced by parent cells e.g. Adrenocorticotrophic hormone (ACTH) secreted by medullary thyroid carcinoma, pheochromocytoma or oat cell carcinoma. The third group includes multiple endocrine neoplasia (MEN) in which two or more endocrine glands are neoplastic in the same individual. MEN-I involves pancreas, pituitary and parathyroid glands. MEN-II involves C-cell of thyroid, adrenal medulla and parathyroids. **(Welbourn; 1977).**

There are many syndromes accompained by apudomes such as hypoglycaemia, Zollinger-Ellison-syndrome, Verner-Morrison , Cushing, Carcinoid and Multiple endocrine neoplasia syndromes **(Walter and Isreal , 1987).**

Aim of the Essay :

APUDOMA is a newly discovered group of neoplasms. With the help of the progress and advancement specially immunoassays and highly specific techniques for localization made it possible for many cases to be recorded, although they still rare. This essay is devoted all apudomas yet have been recorded, their early diagnosis and proper managment.

It is important and interesting to the medical professors to be alert to the fact that apudomas manifest clinically by systemic manifestation more than local effects. This is due to circulation of amines or polypeptides which they secrete. Similarity it is important to notice the familial incidence of the disease and the relationship of glands involved in the same person.

APUDOMAS AND APUD CELLS

Many recent studies show the development and biology of Apudomas and have developed in parrallel with the understanding of the endocrine system and its relationship with the nervous systems and then more recent work was done by **Pearse 1968** and lead to identification of the cell of origin of peptide hormone calcitonin. He found that parafollicular cells of thyroid is the source of calcitonin. During the course of these studies Pearse found that C-cell of thyroid has a number of cytochemical and ultrastructural properties with the peptide hormone producing cells of other organs like islet of pancreas, G cell of stomach and many APUD cells (mentioned before) **(Welbourn , 19 7).**

History of APUD system :

The story of the APUD cell system can be thought to have started when **Nonidez (1932)** showed that (C-cells) of thyroid contained argyrophile granules and suggested they were the antecedent of an endocrine secretion poured directly into blood vessels.

Later **(Copp et al., 1962)** showed the existence of a calcium lowering hormone (eventually called calcitonin) but thought it originated in the parathyroid glands. Subsequently **Foster et al., (1964)** demonstrated it originated from thyroid **Pearse, and Bussolati; (1967)** showed unequivocally by immunofluorescent localisation that the cells of the origin of calcitonin were Nonidez's cell, (C-cells of thyroid).

Pearse (1966) thoroughly investigated the cytochemistry of the C-cell and found it had a number of cytochemical and ultrastructural characteristics in common with other, apparently unrelated, polypeptide hormone-producing cells. This suggested to him that all the cells in the vertebrate which posses these characteristics formed a distinct class of cells which he called the APUD system **(Pearse; 1968)**.

General characteristics of APUD system :

Cytochemically, the ability to synthesize and store catecholamines after uptake and decarboxylation of exogenous amine precursors, are the most important and true specific characteristics and according to, APUD cells are named, and any cell has these characteristics is put in this category, this properity led to the introduction of the name APUD for these cells . The presence of choline esterase , non speicific esterase, alpha glycerophosphate dehydrogenase and endogenous aromatic amines were also variable cytochemical properties, **Pearse and Welbourn (1973)** found these last characteristics not considered a true specific for APUD cell but is an essential stage in identifing of these cells and present in animal species and different APUD cell subtypes **(Pearse and Welbourn 1973)**.

Embryologically, **Pearse (1966)**, compared the cytochemical features of APUD cells in the thyroid, pancrees and pituitary to features of cells known to be of neural crest origin and suggested "the amine storing mechanism and the presence of cholinesterase together point towards a

common cell of neural origin" perhaps coming from neural crest of the neuroectoderm. Neuroectoderm cells migrate with endoderm into ventral direction into foregut, midgut and some residue in derivation of thyroid, thymus, and lung, the cells of adrenal medulla and extra adrenal tissues, skin melanocytes, carotid body, come from similar source **(Pearse 1968).** The list of APUD cells was expanded to include amine and polypeptide producing cells throughout the body, with this expansion of the list of APUD, it was recognized that synthesis of peptide secretory products was a more constant functional indicator than synthesis of amines **(Pearse and Polak 1971).**

Ultrastructurally, the most characteristics features was the presence of membrane-bound intracytoplasmic granules which proved to be the sites of both amines and peptide storage and which stained to a variable degree with histologic stains containing silver salts and other reagents **(Pearse 1968).**

There are some less important features as low levels of rough endoplasmic reticulium, high level of smoth endoplasmic reticulum, high contienty free ribosomes and prominent microtubules and centerosomes. These ultrastructural features are not specific because many cells have the same features and not APUD as protein secreting cells **(Pearse 1968).**

The Following are APUD cells :

1- <u>G-cells (gastrin secreting cels) of the stomach</u> :

They are in the lateral walls of the antral glands portion of gastric mucosa. But in some patients with gastric hypersecretion, G-cells undergo

hyperplasia and occupy the whole length of pyloric portion. The cells are large and round or oval in shape with a broud base, containing many gastrin granules and a narrow apex that reaches the mucosal surface. Microvilli project from the apical end into the lumen. Receptors mediating gastrin responses to changes in the gastric contents may be present in the microvilli **(Gangon ; 1985).**

2- **VIP secreting cells (vaso active intestinal peptide)** :

They are found in the gland cells of nerves of gastrointestinal tract. The glanc cells are mainly in the small intestine specially the jejunum and duodenum. They are vary in size and shape (simple tubular and simple branched tubular) **(Gangon ; 1985).**

3- **Argentaffin cells (D, EC, S & EG)** :

They are found throughout the gastro intestinal tract. They are located chiefly in the basilar portions of the gastric glands and the crypts of Lieberkihn and are numerous in the appendix and terminal ileum where form five to ten cells in cross section may be seen in each crypt. They are pear-shaped, being broudest at the base which rests on the besement membrane and the apex of the cell is directed toward the lumen of the crypt. The nucleis are round and the cytoplasm has granules containing 5- hydroxytryptamine and its precursors. When combined with formalin, these granules have the ability to reduce alkaline silver salts to metallic silver. Also exhibit the chromaffin reaction and sometimes called enterahromaffin cells **(Gangon ; 1985).**

4- Pancreatic islets of langerhans : (A , B & D)

Pancrease is both an endocrine and an exocrine gland included within the same stroma The endocrine component is the islets of langerhans which secrete the insulin , glucagon, somatostatin and pancreatic polypeptide hormones **(Edward and Robert; 1986)**

Islets cells :

They appear as scattered pale areas in the pancreatic lobules. They are common numerous in the tail than in the head They are vary in size, not encapsulated but are morly supported and surounded by delicate reticular tissues which seperate them from pancreatic acini They consists of irregular cords of cells seperated by sinusoidal capillaries, they can be differentiated with stain dyes , by ultrastructrual morphology of their granules and most imp ortantly by their hormonal contents the cells of islets are

Alpha or A cells 20% : (Secrete glucagon). They are larger in size but fewer in numbers and tend to be in groups, they contain large acidophilic granules which dissolve in water but are alcoholic resistance.

Beta or B cells 70% : (secrete Insulin)

They are smaller in size but are the most numerous type, they contain very fine basophilic granules which dissolve in alcohol but are water resistance.

Other types of cells :

C. cells (Chromophbes, 2%). Delta cells 5% (D-cells) have large pale granules with closely applied membrane, secreta somatostatin **(Edward and Robert; 1986)**

5- **C cells of thyroid (Para follicular cells)** :

They form the minority of thyroid cells 2%. They are large, paler than the ordinary cells of thyroid follicles They don't reach the lumen of the follicle but are squeezed between the basement membrane and ordinary cells, tney contains many characteristic granules , they secrete thyrocalcitonin H. **(Timothy. Harrison; 1986).**

6- **Chromaffin cells : Catecholamine secrting cells** :

They are found mainly in adrenal medulla. They are large and vary in shape (columnar, oval, or polygonal) , they are arranged either in groups around blood vessels or in branching and anastomosing cords. They have eccenteric nuclei and basophilic cytoplasm which contain fine granules that have affinity for chromium salts, due to their contents of catecholamines. When fixed in formalin vapour the cells exhibit fluorescence under ultravolat light. There are two types of cells, noradrenaline and adrenaline cells **(Gangon; 1985)** .

7- **Non chromaffin paraganglia (glomus)** :

They are found in the carotid and aortic bodies. They carotid body (glomus) contains of two types of cells, type- I , type- II cells, surrounded

by fenestrated sinusoidal capillaries, the type II cells which are probably glial cells surround type I cells

8- Chromaffin paraganglia (E & NE) :

They are scattered mases of vascular chromaffin tissues (similar to adrenal medulla) they are present in the retroperitoneal tissues, in close releation to ganglia. They produce catecholamines and give positive chromaffin reaction **(Walter and Isreal 1987)**.

9- Melanocytes : (Melanin forming cells)

They are present just under or in between the cells of the basal cell layer of the epidermis. They are large with branching processes. They contain tyrosinase enzyme and cabable of converting tyrosine into DOPA then into dopaquine which is finally coverted into melanin which is transformed into neighbouring epidermal cells. They are distinguished from other types of cells by (DOPA) reaction. They are responsible for skin color **(Walter and Isreal 1987)**.

The following table shows the different APUD cells origin, their cell organs, their products of amines or polypeptides and corresponding Apudomas