ENDOCRINE TUMORS OF THE PANCREAS

Thesis

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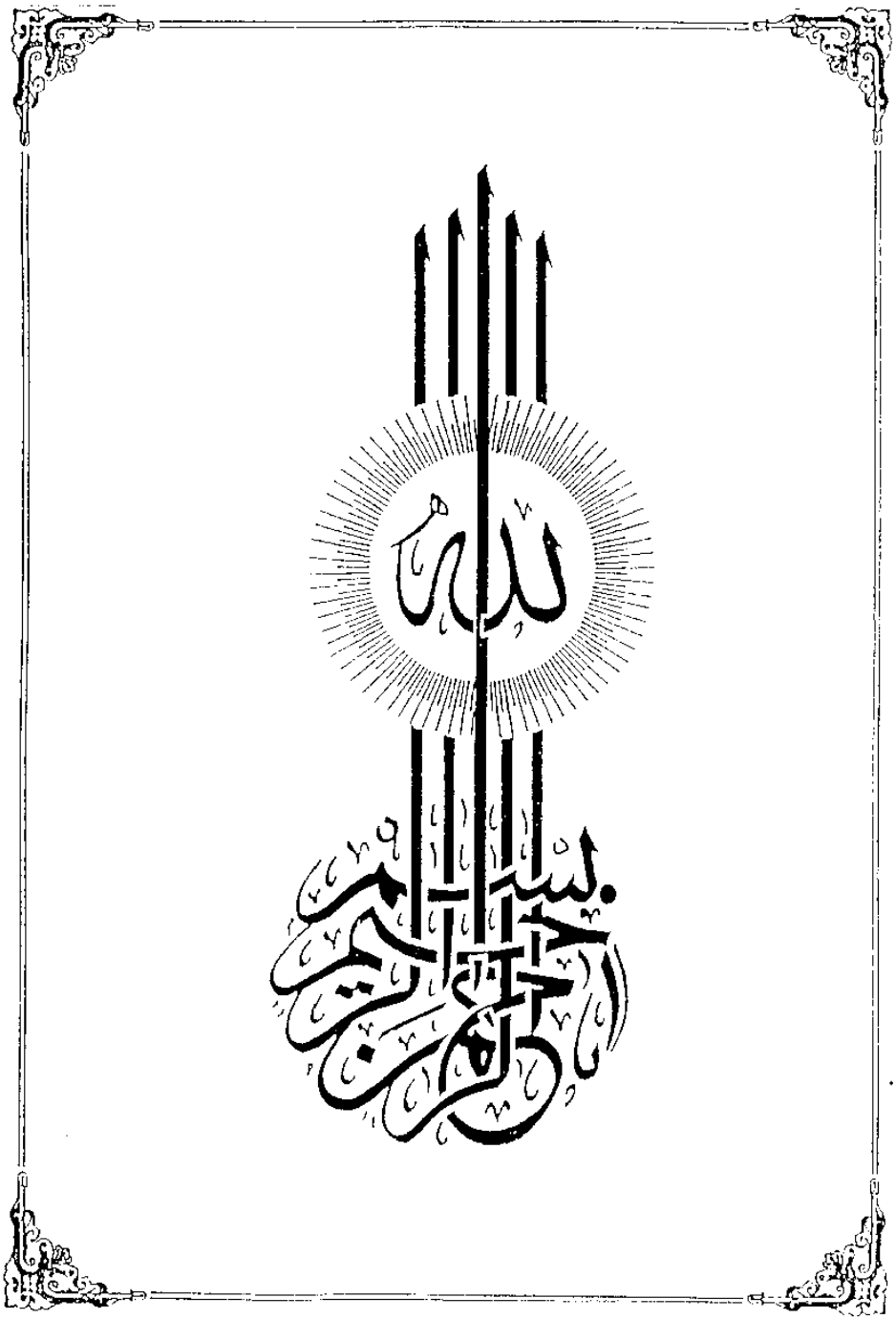

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INTRODUCTION

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Endocrine tumors of the pancreas. The endocrine pancreas is one of the most important endocrine organs in the body.

The endocrine pancreas formed of cells of islets of langerhans constitutes part of the well acknowledged APLLD system. Normally it secretes insulin glucagon, somatostatin and the polypeptide hormone. However, it has the inherent capacity of secreting various peptide hormones.

In the following essay, a study will be done about the tumors arising from the endocrine pancreas.

Emphasis will be directed towards the incidence, pathology, clinical picture, investigations, management and prognosis of the tumors of the endocrine pancreas.

PATHOLOGY OF THE ENDOCRINE PANCREATIC TUMORS

INSULINOMA

Pathology

Incidence and epidemiology

Beta cell insulin tumors were the first islet cell tumors to be described, and for many years were the only hormone producing islet cell tumors known. Insulin producing tumors are by far the most common type of islet cell tumor *(Bloodworth, 1982).*

There are no known precursor states leading to the sporadic development of insulinomas, the less common familial pattern of genetic instigations is observed as an autosomal dominant trait in MEA type I (Werner's syndrome). The penetrance is variable however so that islet cell involvement in MEAI more commonly surfaces as a gastrinoma than as an insulinoma or a pancreatic polypeptide apudoma *(Maingot, 1985).*

Anatomic Considerations

Insulinomas are located in almost equal number through the head (32%), the body (30%) and the tail of the pancreas (34%), those of the uncinate process (3%) only about 1% of insulinomas are ectopic in location but are found close to the pancreas. Some may be located within the duodenal submucosa. Selective angiography demonstrated a tumor supplied from the first branch of the jejunal artery and duodenoscopy revealed a submucosal tumor at the third portion of the duodenum. The acid extract of the tumor contained 1.2 u/gm of insulin and this insulin analysed by reverse phase high pressure liquid chromatography, revealed that it had the same amino acid structure as that of human insulin *(Miyazaki, 1986).*

Ectopically functioning tumors that secrete insulin or insulin like substances are exceedingly rare, reported only in the adrenal, liver lung, kidney, ovary, cervix and mesodermal tissues. The latter tumors which include large fibrous mesotheliomas and fibrosarcomas are more frequent than the former. Extraction of these tumors has been shown to demonstrate an insulin like activity on bioassay but not on immunoassay, the humoral substance is probably a somatomedin and not insulin.

Insulinomas tend to be smaller tumors in most instances, 40% are one centimeter or less in size, few insulinomas are about 5 cm or greater. Most insulinomas are single while multiple insulinomas are found in about 10% of cases. Multiple sites of islet hypersecretion of insulin may take the form of metastatic islet cell carcinomas, multiple adenomas, microadenomatosis, islet cell hyperplasia and nesidioblastosis in decreasing incidence. About 84% are benign while 16% are malignant, only 5% demonstrate metastasis *(Kaplan, 1979)*.

Gross and microscopic Pathology

The tumors vary from soft to firm and from grey white to grey yellow, grey mottled, red or deep red. The deep red tumors are easily mistaken for accessory spleens. Since the gross appearance and location are so variable and significant tumors can be small, the use of selective angiography may be very helpful in guiding the surgeon. About 75% of beta cell tumors are encapsulated and orderly and are clearly benign. About 5-10% of beta cell tumors have metastasis at the time of diagnosis and are clearly malignant. This leaves 15-20% of tumors in which the determination of malignancy can not be made. The tumors appear locally invasive but without other evidence of carcinoma *(Steven, 1983)*.

The distinction between benign and malignant tumors without a capsule is usually not possible on histologic grounds since islet cell carcinomas seldom have anaplastic or pleomorphic nuclear, and mitoses although present are not frequent. The diagnosis of malignancy usually depends upon the documentation of perineural invasion, lymph node invasion or hepatic metastasis *(Grage, 1980)*.

Islet cell tumor nuclei are round or ovoid with a distinctive fine, stippled chromatin pattern and an inconspicuous nucleolus.

The cytoplasm may be scanty or abundant and varies from opaque to granular. An occasional islet cell tumor and abundant acidophilic cytoplasm, metastatic to the liver may be mistaken for a hepatocellular carcinoma despite the difference in nuclear structure.

There are several patterns of growth in beta cell tumors, the serpentine cord-like pattern being the most distinctive. In the tumors or within the same tumor, the cells may form solid clusters, a gland-like pattern or a rosette-like pattern centered around blood vessels. The stroma is vascular but often contains considerable hyaline, really a variant of amyloid *(Reid, 1982)*.

In microadenomatosis, the pancreas is enlarged and diffusely involved. The microadenomata may be little larger than a normal islet of Langerhans, but usually vary in size from 0.2 to 5.0 cm in diameter *(Le Quesne and Daggett, 1983)*.

ULCEROGENIC TUMORS OF THE PANCREAS

History

The gastrinoma syndrome or the Zollinger Ellison syndrome (Z.E.S.) associated with the presence of an ulcerogenic islet cell tumor of the pancreas was first described in 1955 and is now recognised to be second in frequency to the insulinoma syndrome. The suspected presence of these functioning pancreatic tumors is usually confirmed by specific radio immunoassay. The original description of the gastrinoma was based upon a study of two patients operated upon between 1952 and 1954. At first, it was suggested that glucagon might be responsible for the observed syndrome. Gastrin was not implicated until the isolation of gastrin like substance in 1960. It was proved that the secretagogue produced by the islet cell tumors and their metastasis was gastrin in amounts 35 times greater than these produced by similar weights of porcine antrum *(Gregory et al., 1960).*

It is thought that the gastrin in these pancreatic tumors arises from the pancreatic D cell. Most of the tumors are multifocal within the pancreas and about 60-75% are malignant with metastases at the time of presentation *(Martin, 1974).*

Pathogenesis

Without a tumor, gastrin is not present in the adult pancreas but can be found in the fetal pancreas.

Various biologically active forms of gastrin have now been identified. They range from big (G 36), little (G 17) and mini (G 14) gastrins. REcently, a larger gastrin called big big gastrin has been reported. The majority of

patients with gastrin producing tumors have a greater quantity of G 34 than G 17 in their plasma *(Mac Loual, 1982).*

There are patients who exhibit the clinical features of Z.E.S. who do not have gastrinoma tumors of the pancreas or duodenum. Such patients have an antral mucosal source of their hypergastrinaemia. By definition, the similar clinical picture associated with an antral mucosal origin without tumor can not be accurately designation of pseudo Z.E.S. (Ps. Z.E.S.). More recently, a physiologic designation has been ascribed to the same clinical picture with hypergastrinaemia of antral origin as non tumorous hypergastrinaemic hyperchlorhydria (NTHH). It was postulated that there is an overactivity mucosa. Moreover, from a pathologic viewpoint, the antral source of hypergastrinaemia has been reported as one of two types of Z.E.S., namely antral G cell hyperplasia (AGCH), as contrasted to tumor gastrinomas, based on immunocytochemical techniques.

Pathology

Unlike insulinomas, at least 60 per cent of gastrinomas are malignant and half of the patients have metastases at the time of initial diagnosis. Thirty per cent of patients have identifiable, resectable benign adenomas, but solitary lesions limited to one anatomic area of the pancreas occur in only half. Among pancreatic tumors, the anatomic site of the tumor is distributed in a head-body-tail ratio of 4:1:4. Thirty per cent of patients have more than one area involved, and the entire gland may be diffusely involved in about 20 per cent of patients. Fewer than 25 per cent of all patients (regardless of biologic type of or location of tumor) will have a single lesion. *(Townsend and Thompson, 1986).*

Although the pathologist can confirm the presence of gastrinoma, a major problem exists. There are no reliable morphologic criteria of malignancy. In the absence of visible lymph node or liver metastasis, this is very difficult to determine. Most endocrine tumors of the pancreas and duodenum are histologically heterogeneous, cytologically bland and without microscopic characteristics that permit confident prediction of malignant biologic behaviour. Because the malignant potential of the tumor can not be determined by histologic examination in the absence of demonstrable metastatic disease, only the clinical course of the patient, truly defines which tumors are, in fact, malignant. If tumors metastasize, they are malignant. If we define malignancy by persistence of tumor-produced gastrin after some tumor tissue has been resected, a great majority of patients can be considered to have malignant tumors. Fewer than 15 per cent have a "cure" as defined by normal post operative serum gastrin levels. If a patient has normal levels for a year after operation, we consider him cured. It was also found that disseminated disease is more likely to be present in patients who have relatively high concentrations of the 17 amino-acid form of gastrin (G 17) (> 20 per cent of total gastrin), and that the percentage of G 17 is low early in the course of the disease and increases as the tumor enlarges or as metastases occur. In consequence, it is suggested that the percentage of G 17 may serve as a marker for staging the disease *(Townsend and Thompson, 1986).*

The discovery of gastrinomas in unusual locations such as lymph nodes, poses a diagnostic problem centered on whether the neoplasm is primary or metastatic. These extragastroenteropancreatic (EGEP) gastrinomas have many of the features of gastrinomas in conventional locations. However, the centrifugal expansile growth pattern characterized by a thick fibrous capsule, hyalinized fibrous septa and frequently cystic

degenerative changes in EGEP gastrinomas should alert the pathologist to the probability that these neoplasms are primary. Additional evidence for the primary nature of these EGEP gastrinomas is derived from the postoperative normalization of high serum gastrin levels *(Bhagavan et al., 1986)*.

GLUCAGONOMA

History and Epidemiology

The third major clinical syndrome associated with islet cell tumors results from the elaboration of glucagon and is sometimes referred to as the hyperglycemic, cutaneous syndrome.

Glucagon was identified and named in 1923 by Kinball and Murlin who recognized its physiologic properties. However, it was not until 1966 that Mc Grawan and associates described the prototype patients, which established glucagonoma syndrome as an entity.

A literature review in 1978 revealed 47 case reported of the glucagonoma syndrome, six of which had been reported prior to the McGravan publication. Patients in this series were between the ages of 20 and 73 years with a sex ratio of 28 females to 19 males.

Anatomic Considerations

From the descriptions of the tumor, it would appear that the majority (30) arose in the body and tail of the pancreas, although it should be remembered that this was also thought to be true for insulinoma until a large number has been reported *(Higgins, 1979)*.

In many instances, the tumor was extensive and metastases were evident at the time of diagnosis, although in 18 of the reported patients the tumor was noted to be confined to the pancreas. The absolute incidence of true malignancy is not clear. It has been suggested to be in the order of 60% *(Macdonald, 1982)*.