INTRODUCTION AND REVIEW OF LITERATURE

The endocrine cells of the pancreas are found in scattered groups throughout the organ and are commonly designated as islets of Langerhans or simply as the pancreatic iselts or islands.

These occur as clusters of a few to hundreds of cells embedded in the acinar tissue.

Occasional single iselt cells may be found among the exocrine secretory cells of the pancreatic acini.

The disribution of islets is variable, but in man they are more numerous in the tail of the organ.

It has been estimated that approximately one million islets are present in a human pancreas (Keel and Neil,1974).

The islet is highly vascular with numerous capillaries that probably touch every endocrine cell. In contrast, the acinar tissue is rather poorly vascular.

In routine histologic preparations, the islet cells show no strikingly individual characteristics. They appear as groups of lightly stained cells surrounded by a thin layer of reticular fibers. However, appropriate fixation and staining techniques reveal the presence of several cell types (Ross and Reith,1985).

The two most common are the larger spindle-shaped alpha or A-cells which compose about 20% and the smaller beta or B-cells which compose about 75% of the islet cells. The A-cells are sometimes absent in the smaller islets and when present tend to be located peripherally (Greep and Weiss, 1973).

Both cell types contain characteristic secretory granules whose relative solubility originally distinguished A-cells from B-cells. The secretory granules of the A-cells are preserved by alcohol- or formalin-containing fixatives whereas the B-cells granules are soluble in alcohol. If both types of granules are preserved by an appropriate fixative such as Zenker formol or Bouin's fluid, differences in the staining affinities of the granules may be seen. A third cell type encountered less frequently (about 5%) contains small granules with still different staining properties. These cells were first found in human pancreatic islets and designated delta, or D-cells. They are most numerous in primates but have been described in many other species. A staining characteristic of some of the D-cell granules is their capacity to reduce silver nitrate to give the argentaffin reaction (Copenhaver and Bunge, 1971). In addition to these cells, a fourth type of agranular, clear cells, the C-cells have been observed in the guniea pig pancreas . The nature and significance of these infrequent cell types in unclear. Various possibilities, such as variations in the secretory cycle or degenerative stages of the A- or B-cells have been suggested to explain the C- and D-cells (Greep and Weiss, 1973).

Pancreatic islands have a rich blood supply and the secretion of these cells passes directly into the capillaries . Insulin, is formed by the B-cells which is essential in carbohydrate metabolism, regulating the blood sugar level. Deficiency of insulin by destruction of pancreatic islands leads to an inability of the body to utilize glucose and to an increase in its amount in the blood accompanied by excretion of sugar in the urine .

Another hormone, glucagon, is produced in the pancreatic islands. It induces glycogenolysis in the liver and thus brings about an elevation of blood sugar. The A-cells are the site of glucagon. D-cells secrete somatostatin which has potent inhibitory effects on various secretion processes in pituitary , pancreatic and gastro-intestinal tissues. In addition, it is probably a neurotransmitter in the central nervous system. The various biological actions of somatostatin seem to be mediated through specific high affinity receptors (Bloom and Fawcett, 1968 and Mavrer, Kilijn, Stefanko, Blaauw and Blakenstein,1986).

The history of the islets from the date of their discovery was chiefly interesting for the controversies in the opinions about their nature and function.

The structure of the islets was first described by Langerhans in 1869. Henceafter, a good deal of work has been done

on their morphology (Laguesse, 1901; Lane, 1907; Bensley, 1911; Bloom, 1931 and Thomas, 1937). Besides, histochemical studies were also done by Pearse (1968).

In addition, some quantitative studies on the islets and their cells were done by Opie (1900); Bensley (1911); Overhalser (1925); Thomas (1937) and Haist and Pugh (1947).

Kuhne and Lea (1869) gave them the name of "intertubular cell clumps". They were then called "points follicularis" by Renaut (1879). Few years later, the name "les islets de Langerhans" was applied to them by Laguesse (1896) and "islets of Langerhans" by the American Anatomists (Lane, 1907).

Langerhans (1869) himself believed them to be the end apparatus of nerve fibers. However, Renaut (1879) considered them lymphoid tissue in the substance of the pancreas .

After several studies on the islets of Langerhans in viper snakes and in sheep, Laguesse (1901) reported that the cells of the islets contained granules which probably were regarded as metabolic products of the cells themselves.

Later, several authors (Lane, 1907; Bloom, 1931; Thomas, 1937 and Ham, 1969) described the cells of the islets of Langerhans in different animals. They found certain differences

in the morphological characters of the A, B, C and D-cells of the islets. According to these authors, the A-cell by Heidenhain's Azan stain was polygonal in shape and its nucleus was usually elliptical, markedly vesicular, large and its chromatin content was very small. The chromatin was distributed into few small, spherical masses and this contributed in section to the lucid vacuoles and the prominent appearance of the nucleus of these cells. In some cells the cytoplasmic granules were distributed throughout the entire cytoplasm. In others, the granules were clumped into a mass at the cell pole close to the capillary, while the remainder of the cytoplasm was comparatively or completely free of them.

In sections stained with neutral gentian violet, the A-cells appeared polygonal in shape and stood out clearly against the lighter and yellowish background formed by the mosaic of the B-cells. In point of number, the A-cells ranged next to the B-cells (Walter, 1944).

The B-cells, by Mallory's aniline blue stain were much more numerous in the islets. Entire cords of them were seen uninterrupted by the A-cells. The nucleus of the B-cell was circular and centrally placed inside the cytoplasm. It was smaller and markedly less vesicular than the nucleus of the A-cell and it contained a richer amount of chromatin. The

latter was usually seen in the form of fine strands forming a network. The cytoplasm of the B-cells was packed with violet granules which were uniformly distributed around the nucleus.

The D-cells, by Mallory's analine blue stain, were the least numerous of all the islet cell types. They were nearly equal in size to the B-cells and were filled with specific granules. The granules were the same or slightly larger in size than those of the A-cells. In size and shape, the nucleus of the D-cells were usually scattered among the A, B, and C types and were rarely seen in groups of more than two cells (Bloom, 1931; Thomas, 1937 and Ham 1969).

The Bensley's (1911) undifferentiated cells (C-type) were the smallest of the islet cells and were present less frequently than the other types. They might be identified by their small size, their lack of any specific granulation, their very light colour or almost clear appearance after staining and also by their elongated nuclei which contained little chromatin. They were scattered among the other types of islet cells.

B-cells with modified Aldehyde fuchsin were characterised by specific fine purple violet granules evenly distributed in the cytoplasm. The nucleus was rounded, central in position and rich in chromatin.

The cytoplasm of the A-cell was characterised by yellow granules which were not evenly distributed, the nucleus eccentric and more vesicular than B-cell.

The cytoplasm of D-cell was characterised by green granules and the nucleus was deeply stained (Copenhaver and Bunje, 1971; Drury and Wallington, 1980 and Kelly, Wood and Enders, 1984).

Walter (1944) offered a basic pattern for the origin of islet tissue in the rat which possibly could be common to all mammals. He found that in the embryonic and early postnatal stages of development, the islets originated from three and possibly four sources as distinguished by their position with respect to the developing duct system.

The first islets differentiated in the 13 days rat embryo from the wall of the solid pancreatic cord. These islets did not exceed three or four in number. Their position suggested a certain similarity in origin to those found in the lower vertebrates.

The majority of embryonic islets took origin from the pancreatic tubules. This type of islet origin was first seen in the fifteenth day but the most active production occured from 16 to 18 days.

The embryonic islets persisted in the postnatal animal and , in the adult, were represented by the larger interlobular and intralobular islets.

During the first week of postnatal life there was a considerable increase in the formation of new islets. These islets arise from two sources; the majority originated from the terminal portions of the secretory duct system at the base of acini. Occasionally, they were observed within the acini proper. A lesser number of islets were developed from the larger ducts similar to those formed in embryonic periods.

Some evidence indicated that the secondary duct system, or tubules, actively produced islets in postnatal life. In addition these tubules established contact with the persisting embryonic islets and contributed more cells, particularly of the alpha type, to the periphery of the islets.

The B-cell was the only islet cell type to differentiate during embryonic development. Beta granules were first distinguished in the islets during the nineteenth day of foetal life in the rat.

Cytological evidence indicated that secretory activity began in the B-cells after the twentieth day. This was limited

to exceedingly few cells and no increase in secretory activity occured until parturition. Instead, the majority of cells were in the production and storage phases of the cycle.

A-cells were first recognized during the second day of postnatal life. The number of cells were few per islet and contained small quantities of granules.

Some A-cells appeared to be actively secreting by the fifth day of postnatal life. The majority of such cells were in newly differentiated islets. Few cells in the persisting embryonic islets were actively secreting at this time. The majority of the A-cells in the persisting embryonic islets took a longer time to reach their mature state than the A-cells in the newly formed islets. Secretions from the B-cells might play some part in embryonic metabolism after the twentieth day of embryonic development.

In the first day postpartum the only granular cells in the islet are usually confined to a single cord or to small nests at the islet periphery. These are to be recognized as A-cells and the alpha granules appear during the second day in these cells.