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THE OCCURRENCE OF GIANT BETA ISLETS IN THE PANCREAS OF THE CALF

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INTRODUCTION

During the course of correlated microscopic and electron microscopic studies of pancreatic islets of calves, extremely large islet masses were encountered. They consisted almost exclusively of beta cells. This fact necessitated a preliminary study of the occurrence and characteristics of the large islets in order to avoid confusing them in electron microscopic studies with the regular islets. Trautmann and Fiebiger stated in their study of size and distribution of islets that the majority of pancreatic islets were between 0.04-0.2mm. in diameter, and that the average number of islets was 125 per 50 sq. mm. in the pancreas of the calf(Trautmann, '41). The largest islet recorded as occurring in vertebrates was reported by Wilkinson in a 7-month dog and measured 333μ in diameter (Wilkinson, '58). He reported further that there appeared to be no significant changes with age in the size and distribution of islets. Other workers, however, claim that both the number and size of pancreatic islets increase as the age increases (Haist, '48).

It is generally agreed that the duodenal portion of pancreas contains more islets per unit area than any other portion, and Wilkinson stated that the duodenal portion showed an overall superiority in size of islets. Many workers have reported on the cellular components of the mammalian islets of Langerhans. According to Pochon, the A-B cell ratio in the cow is 1:20 by volume or 4-96 by number, and alpha cells are reported to be usually scattered throughout the islets (Pochon and Gomori, '39). It is also known that alpha cells are more prevalent in small islets.

In the present study, using the calf, attempts were made to determine: (1) the distribution and size of giant beta islets as well as regular islets in different portions of the pancreas: (2) the histological structure of giant beta islets, and (3) the cytological characteristics of giant beta islet cells compared with those of regular islets.

MATERIALS AND METHODS

In the work to be reported ten Holstein calves were used, and the ages varied from 2-4 months. The calves had been subjected in other experiments to the administration of glucagon, insulin, nicotine, and reserpine. The details of treatment are omitted here, and will be published later, since there was no evidence that the treatments had affected the general structure of the large islets.

The duodenal, middle, and splenic portions of the pancreas were removed immediately

after the animals were sacrificed, and fixed for 24 hours in Bouin's fixative. The tissues were then dehydrated in 3 changes of dioxane, and embedded in parffin. The paraffin sections were cut at 7 microns and stained with Gomori's Aldehyde Fuchsin staining for islet cells (Lansing, '55). Serial sections were made and mounted in the usuall manner to ascertain the overall structure of large islets. For cytological study of large islets, 50 nuclei of giant islet beta cells and those of regular islets were measured respectively by routine photographic methods and also by the paper weight method. The Golgi images, extent of granulation of beta cells, and other cytological characteristics were also studied.

In counting pancreatic islets, those under 200μ in diameter, were arbitrarily regarded as reguler islets, those 200-500μ as intermediate, and those above 500μ as giant islets.

OBSERVATIONS

1. Size and Distribution

The study of pancreatic islets shows that the islets range from less than 50μ to 1,395μ in diameter. A giant islet of 2.7mm. in length was found. The duodenal portion of pancreas showed superiority in the number of large islets as is the case with regular islets. The middle and splenic portiont follow in this order. In agreement with other workers, the authors found that regular-sized islets have similar distribution. The percentage of islets above 200μ in diameter was approximately 2% in the duodenal portion, 1.8% in the middle, and 0.8% in the splenic portion (table 1). The average percentage of giant islets including those above 200μ in diameter versus regular islets is 1.8%. The number of pancreatic islets contained in 50 sq.mm. was 191 on the average (table 2).

Table 1. Average Diameter of Islets (1 longitudinal measurement and 1-4 cross sectional measurement)

	Regular			Intermediate	Giant
	-75μ	75-100μ	100-200μ	200-500μ	500-1000μ or above
Splenic portion	84.5%	8.5%	6.2%	0.6%	0.2%
Middle portion	88.3	7.4	3.0	1.1	0.7
Duodenal portion	85.0	8.0	5.0	1.4	0.6
Average	85.9	7.9	4.7	1.05	0.5

Table 2. Distribution Count (Islets/50 sq. mm.)

	Splenic portion	Middle portion	Duodenal portion	Overall average
Minimum	106	109	133	116
Maximum	291	265	281	279
Average	180	194	200	191

2. Histological Structure

Most giant islets are located within the lobules of the pancreas, but a few are located in the interlobular connective tissue and capsule (fig. 1,2,3,4,5). The shape may be ovoid,

spherical, elongate, and consists of irregular clumps or cords of beta cells (fig. 6, 7, 9). Giant islets enclosing acinar tissue are also found (fig. 7). Relatively abundant areolar-reticular connective tissue surrounds the entire islets, and conspicuous trabeculae of interstitial connective tissue is especially rich around the large blood vessels and duct-like structures(5, 8, 9). The giant islets are markedly vascular compared with the regular islets. The intercalated duct-like structures made up of simple squamous epithelium are found within the trabeculae along with blood vessels (fig. 8, 9). The development of new regular and giant islets is observed. The regular islets are seen to be formed around the terminal pancreatic ducts, and in the formation of giant beta islets, the cells of duct system seen in and around the islets are regarded as the source of new additions of islet cells (fig. 10, 11, 12). The islets of intermediate size also consist almost entirely of beta cells (fig. 4). Alpha cells, if found, are usually scattered throughout the islets. They are grouped into small discrete bodies, and are usually more numerous near capillaries (fig. 6).

III. Cytological Characteristics

The beta cells of giant islets vary in shape due to a packing-in effect: the cells arranged around capillaries are more or less oval or elongate, while those centrally located polyhedral in shape. Boundaries of the cells in active secretory stage are poorly defined in contrast to the sharply defined cells in the storage phase as in the regular islets, due to the difference in the grunular content.

The nuclei of beta cells are usually spherical or oval in shape and contain one or two hypertrophied nucleoli and dust-like chromatin substance, which is responsible for the pale staining of the nuclei (fig. 13). The average diameter of these nuclei is 7.8μ which is larger than those of regular beta cells, which have an average diameter of 6.3μ. The nuclear structure of giant islet beta cells is, therefore, in sharp contrast to those observed in the regular islets. The latter also have 1-2 nucleoli, but contain several coarse chromatin masses which stain intensely (fig. 14).

Negative Golgi images located between the nuclei and the secretory surfaces of the beta cells are usually well-defined and more prominent than in the regular islet cells (fig. 15). A few regular-sized islets embedded in the thick interstitial connective tissue or capsule and those intermediate islets located within the lobules are similar in structure to giant beta islets in that they consist exclusively of beta cells. They also show prominent negative Golgi images and have similar nuclear structures. No appreciable structural changes has been found between alpha cells of giant beta islets and those of regular islets.

DISCUSSION

There are intergradations in size between the regular and giant beta islets, and they range approximately from 0.04 to 1.4 mm. in diameter. The percentage of giant beta islets including intermediate size is 1.8%. As with the regular islets, the duodenal portion of the pancreas shows superiority in the number of large islets. The average number of islets including those of intermediate and giant sizes contained in 50sq. mm. was 191, which

figure is high in comparison with that reported by other workers. Though the total percentage of giant beta islets including those above 200μ in diameter is very small, it may be of great significance in terms of volume. For instance, one spherical or oval shaped giant beta islet with diameter of 1,000μ would be equivalent to hundreds of regular islets in volume, and appear to be equivalent in the amount of insulin secreted.

The shape of giant beta islets may be spherical, oval, elongate, or angular, and consist almost exclusively of irregular cords or clumps of beta cells. The unusual vascularity of the interstitial connective tissue trabeculae is noted, also the relatively abundant arcolar-reticular connective tissue which envelops the entire islet. The regular islets are surrounded by delicate arcolar-reticular connective tissue which are only observed with difficulty.

It is said that large islets located within the lobules and intralobular connective tissue arise from the pancreatic duct system in prenatal development. The intercalated duct-like structures observed within the trabeculae of giant beta islets may be the source of new additions of cells to such giant islets. This suggests that giant beta islets increase in size postnatally by a proliferation of terminal duct cells within or around the islets. The evidende of postnatal formation of new islets, both regular and giant, is indicated by the presence of numerous duct cells in and around the islets though the mitotic figures were not found. It is obscure why the giant beta islets are comprised almost entirely of beta cells. This question remains to be solved.

The beta cells of giant islets have prominent negative Golgi images and vesicular nuclei with hypertrophied nucleoli. Beside these features, the secretory granules are concentrated at the secretory surfaces of the cells. These are indications that the giant beta islets are more actively secreting insulin than the regular islets. In view of these facts the authors came to the conclusion that the giant beta islets are contributing much to the total output of insulin in calves. The total number of regular and giant beta islets contained in the entire pancreas of a calf is not known, but it is certain that the presence of such giant beta islets is responsible for low blood sugar level in the cow. It is authors' conviction that the giant beta islets may serve as supplementary source of insulin secretion as these cells appear to be more resistant to the effect of diabetogenic agents.

SUMMARY

The pancreatic islets were arbitrarily divided into three categories according to the size of islets: 1. regular, 2. intermediate, and 3. giant. A giant islet measuring 1,395μ in diameter and another reaching 2,700μ in length were found. The histological and cytological characteristics of giant islets have been studied in 10 Holstein calves along with the distribution of all size in the different portions of the pancreas. The following is a summary of the present work.

1. The average number of pancreatic islets counted in 50 sq. mm. surface of the pancreas of calves was 191 which is a higher figure than the number reported by other workers.

2. There are intergradations in the size of the large islets, which ranges between 0.2–1.4

mm. in diameter. The duodenal portion contains 2% of giant beta islets, middle 1.8% and the splenic 0.8%. The mean percentage of islets above 200μ in diameter is 1.53%.

3. The intermediate and giant islets consist almost exclusively of beta cells, and therefore, they are tentatively named "Giant Beta Islets" and "Beta islets of intermediate size" respectively. Alpha cells, if found, are grouped into small discrete bodies and scattered throughout the islets.

4. The number of giant beta islets contained in any portion of the pancreas is small. Yet, the volume is enormous in comparison with the regular islets. This fact must always be taken into consideration in any study of insulin secretion.

5. The giant beta islets have prominent trabeculae of interstitial connective tissue in which blood vessels of large and intercalated duct-like structures are found. It is assumed that the Giant beta islets increase in size postnatally by the proliferations of terminal duct cells in and around the islets.

6. The prominent negative Golgi images and vesicular nuclei with hypertrophied nucleoli in the beta cells suggest that giant beta islets are in a more active secretory phase than the regular islets.

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抄 錄　　仔牛膵臟의 巨大 beta島嶼에 關한 硏究——

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10頭의 홀스타인 仔牛에 glucagon, insulin 등 홀몬과 reserpine 및 nicotine을 投與하여 그들이 膵臟의 Langerhans 島嶼에 미치는 細胞學的 영향을 電子顯微鏡에 의해서 연구하는 도중 巨大한 크기의 島嶼를 관찰하였다. 이 巨大島嶼들은 上記한 약품투여에 영향을 별반 받지 않으며 거이 beta 細胞들로만 되이 있으므로 보통 크기의 島嶼들과의 혼동을 피하기 위하여서는 그 分布狀態와 細胞學的 및 組織學的 特徵을 究明하는 것이 필요하게 되이 本硏究에 착수하였든 것이며 아울러 膵臟 各部分에 함유되는 Langerhans 島嶼數의 平均値를 算出하였다.

Langerhans 島嶼는 편의상 그 크기에 따라서 直徑 200μ以下의 것을 "Regular islets" 200~500μ까지의 것을 "Intermediate islets" 그리고 500μ 以上의 것을 "Giant islets"라고 이름지어서 구별하였다. 지금까지 알려진 最大의 島嶼는 개에서 관찰된 직경 333μ의 島嶼이었는데 필자는 本硏究에서 직경 1,395μ에 달하는 것과 거리 2,700μ에 달하는 巨大한 島嶼들을 관찰하였다. 本硏究의 結果를 要約하면 다음과 같다.

1. 仔牛膵臟 50平方mm 面積내에 함유되는 Langerhans 島嶼의 數는 平均 191개로서 다른 연구자에 의해서 보고된 數値보다 훨씬 많은 것이었다.
2. 巨大島嶼의 크기는 直徑 200~1,400μ 이며 그 分布狀態는 보통 크기의 島嶼와 마찬가지로 膵臟의 十二指腸部 中間部 및 膵臟部의 順序로 많이 함유 되고있다. 즉 十二指腸部에는 2% 中間部 1.8% 膵臟部에는 0.8%의 巨大島嶼가 함유되어 있으며 직경 200μ以上의 島嶼平均値는 1.53% 이었다.
3. 中間大의 島嶼와 巨大島嶼들은 거이 beta 細胞들로서만 되어있음으로 "中間大 beta 島嶼" 및 "巨大 beta 島嶼"라고 자 자 명명하였으며 alpha 細胞들이 있는 경우에는 작은 細胞集合體를 이루고 島嶼全般에 걸쳐서 散在한다.
4. 膵臟에 함유되고 있는 巨大 beta 島嶼의 數는 적지마는 보통 크기의 島嶼와 비교할때 그 容量은 막대한 것이며 따라서 insulin 分泌量도 많을것이므로 牛膵臟의 insulin 分泌를 연구할 때에는 반듯이 이 事實을 고려해야 한것이다.
5. 불규칙한 索狀의 實質細胞들로된 巨大 beta 島嶼에는 間質結合組織이 풍부하며 그 間質 속에는 비교적 큰 血管과 介在管様 構造物이 들어있다. 巨大 beta 島嶼는 出生후 島嶼內外에 散在하고 있는 外分泌導管細胞들의 增殖에 의해서 發生하며 그 크기도 增大하는 것으로 믿어진다.
6. 巨大 beta 島嶼의 beta 細胞들은 현저한 Golgi 裝置와 肥大한 核小體 및 腸狀核등의 細胞學的 특징을 가지며 이것은 巨大 beta 島嶼가 보통 크기의 Langerhans 島嶼에 비하여 더 활발하게 insulin 을 分泌한다는 것을 示唆하는 것이다. (本抄錄은 大韓獸醫學誌 第一卷 第一號 p.60에 發表되었음)

Figure 1. A giant beta islet located within a lobule of the pancreas (Gi), showing also scattered regular islets (Ri). The pancreatic islet on the left upper hand corner is an intermediate-sized islet (Ii). ×50.

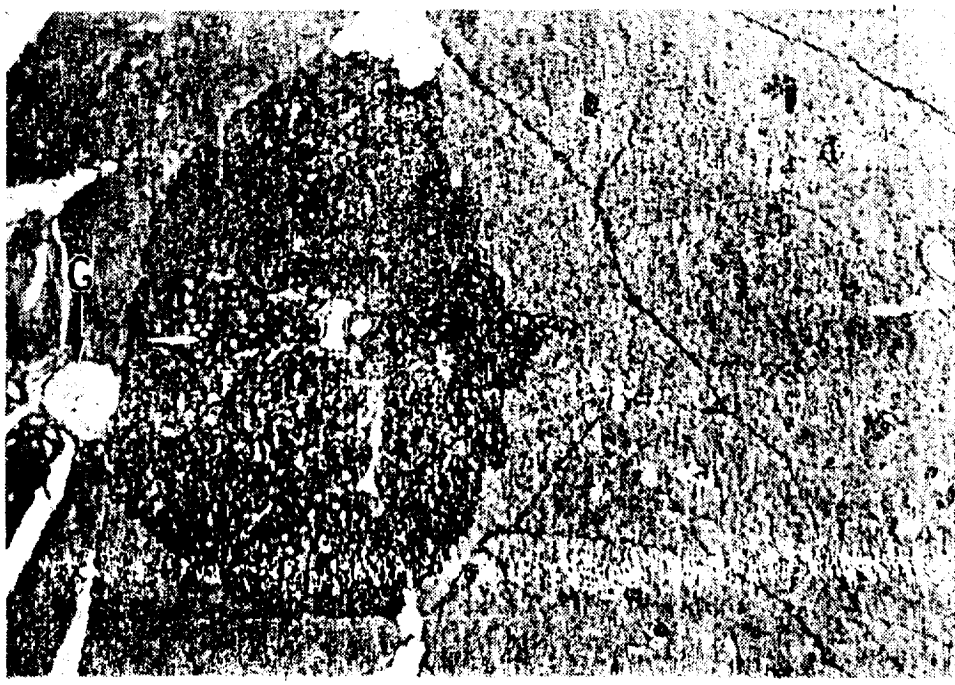

Figure 2. A giant beta islet oval in shape showing prominent vascular structures in the interstitial connective tissue trabeculae. A terminal ganglion (G) is seen close to the giant islet. ×50

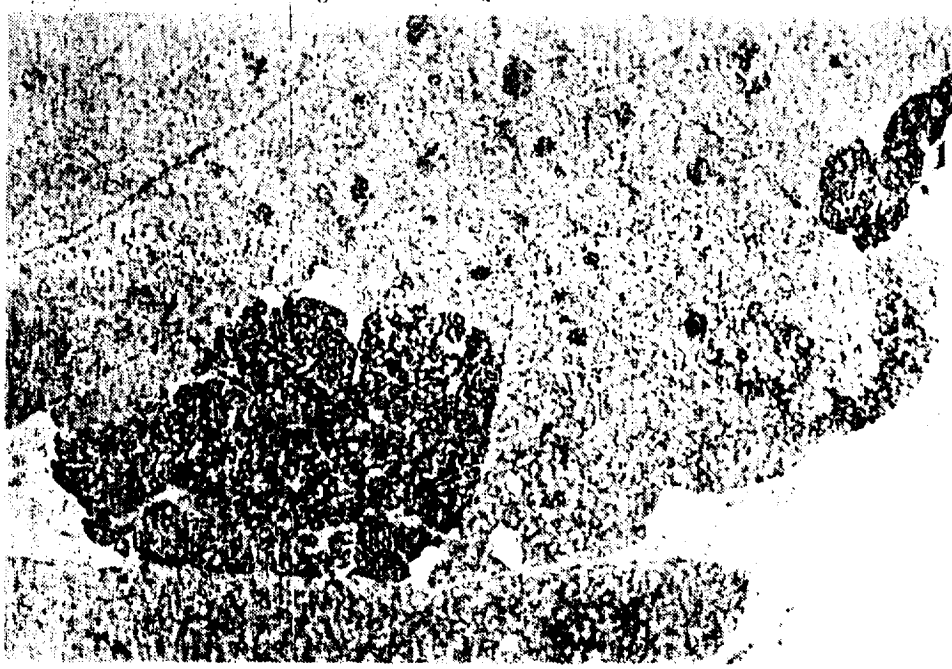

Figure 3. A giant beta islet and an intermediate-sized islet. ×50

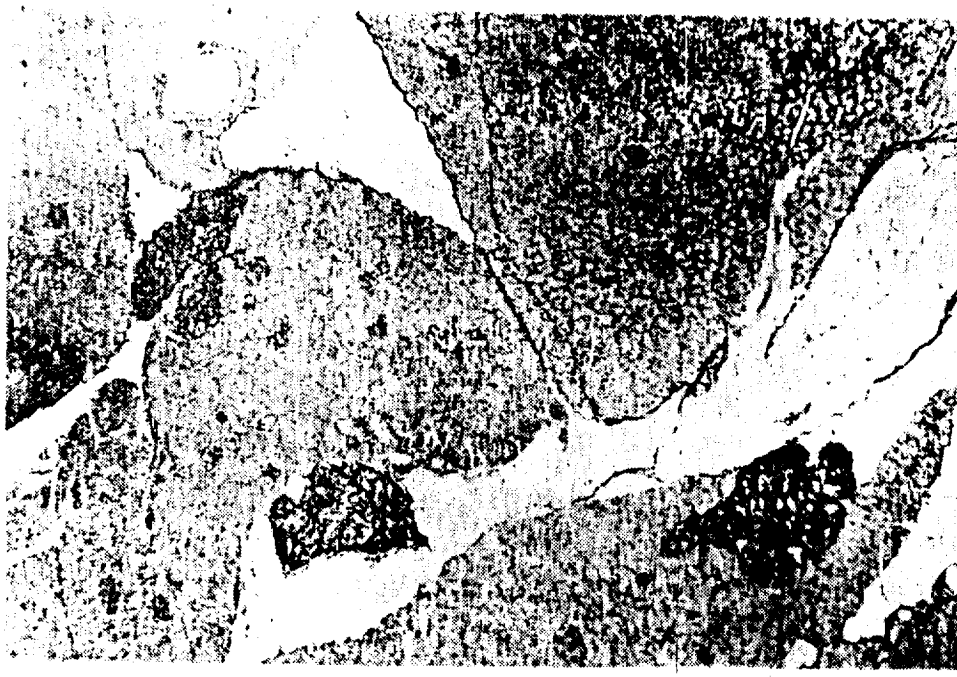

Figure 4. Intermediate beta islets located at the periphery of the pancreatic lobules and in the interstitial connective tissue. ×50.

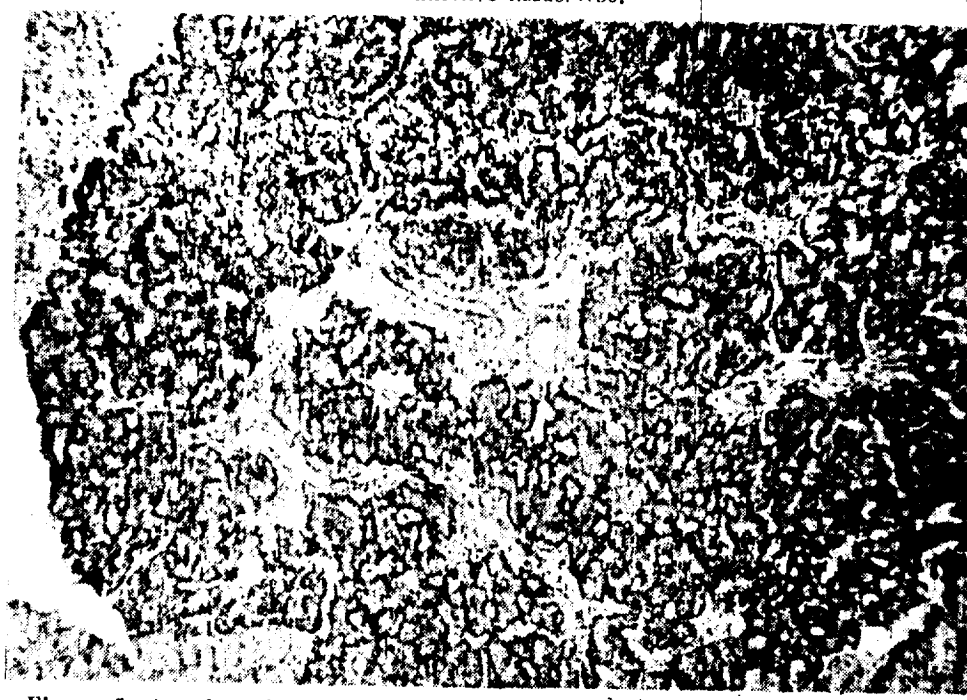

Figure 5. A spherical shaped giant beta islet showing prominent inetrstitial connective tissue trabeculae with large blood vessels and duct-like structures. ×100.

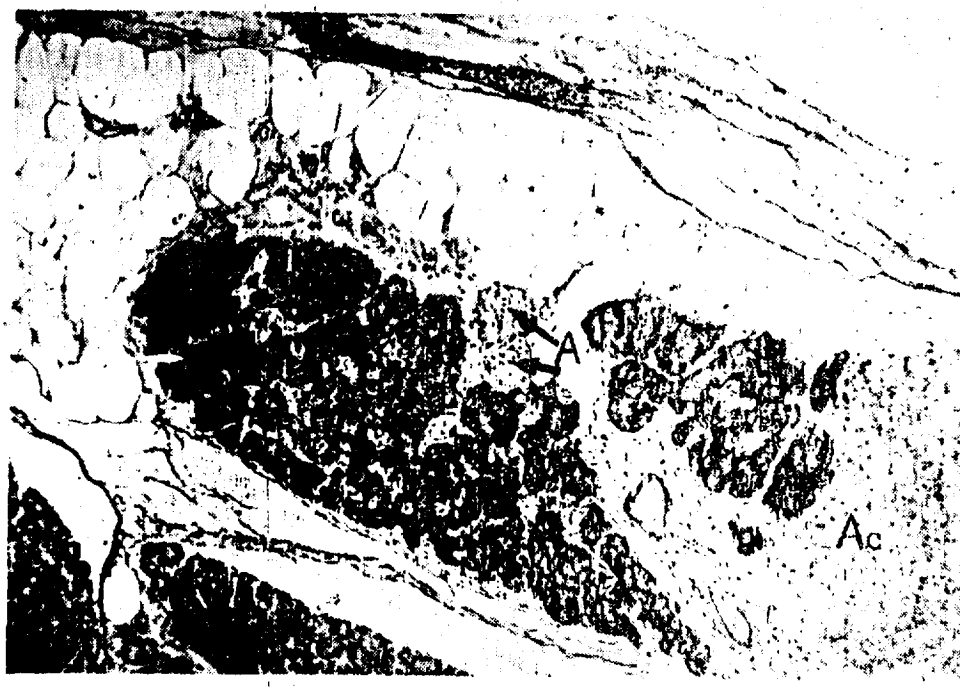

Figure 6. A giant beta islet surrounded by relatively thick interlobular connective tissue septum, showing 2 discrete bodies of alpha cells (A) and 1 slender beta islet embedded in the capsule of pancreas. Acinar tissue (Ac). ×100.

Figure 7. Two angular shaped giant beta islets enclosing acinar tissue. ×100.

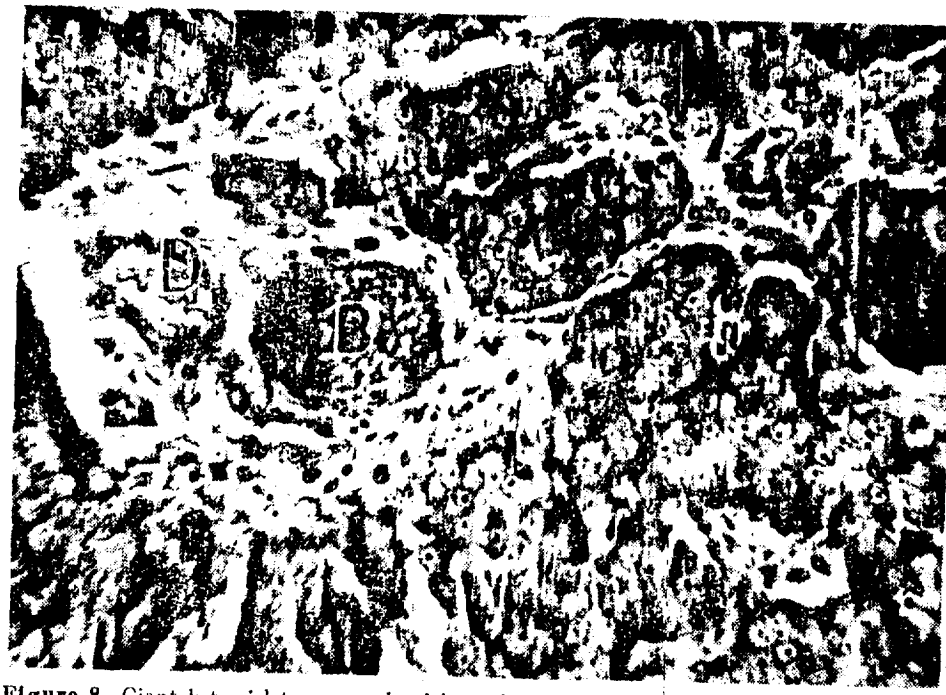

Figure 8. Giant beta islet composed of irregular clumps of beta cells, showing prominent vascularity (B, blood vessel) and terminal duct-like structures (D, duct) in the interstitial connective tissue trabeculae. ×470.

Figure 9. A high power photomicrograph of giant beta islet showing abundant interstitial connective tissue trabeculae with a prominent blood vessel (B) and a duct-like structure (D). Small terminal duct-like structures are also seen (d). ×450.

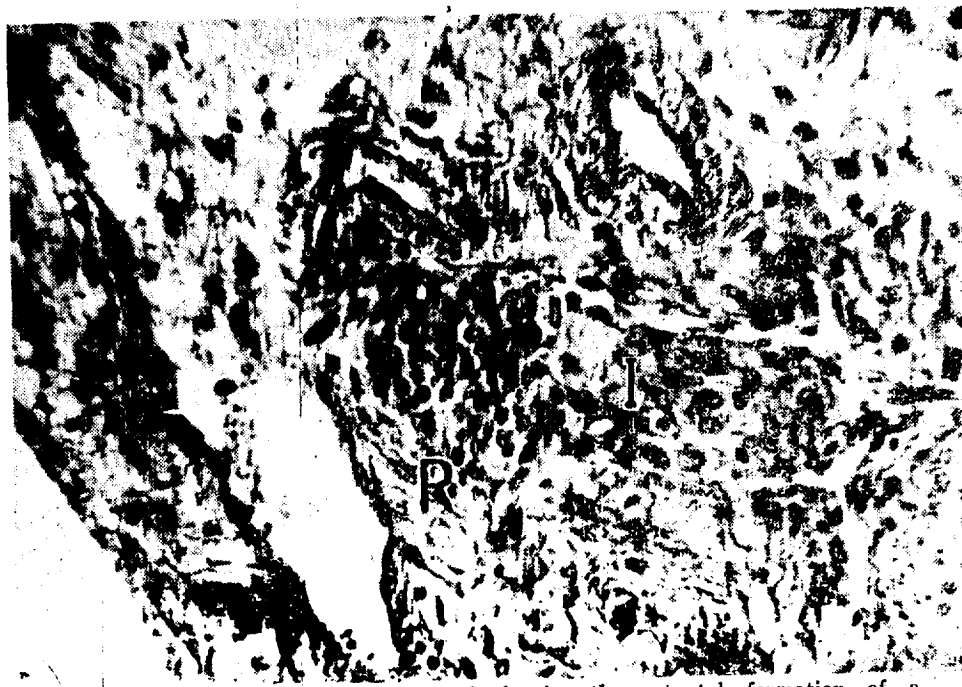

Figure 10. A high power photomicrograph showing the postnatal formation of a regular islet (R) at the end of intercalated duct (I) within the interstitial connective tissue septum. A small number of beta cells show the beginning of granulation. ×470.

Figure 11. A picture showing the growth of a regular islet (R) at the end of intercalated ducts (D). The granular content is less than that of the already formed islet cells in function. ×470.

Figure 12. A high power photomicrograph showing the evidence of postnatal growth of a giant beta islet. Clumps of beta cells are surrounded by the cells proliferated from the terminal duct-like structures (arrows). ×470.

Figure 13. Giant beta islet cells (B) showing large vesicular nuclei with hypertrophied nucleoli and dust like chromatin substance. A group of alpha cells (A) are seen on the right. ×970.

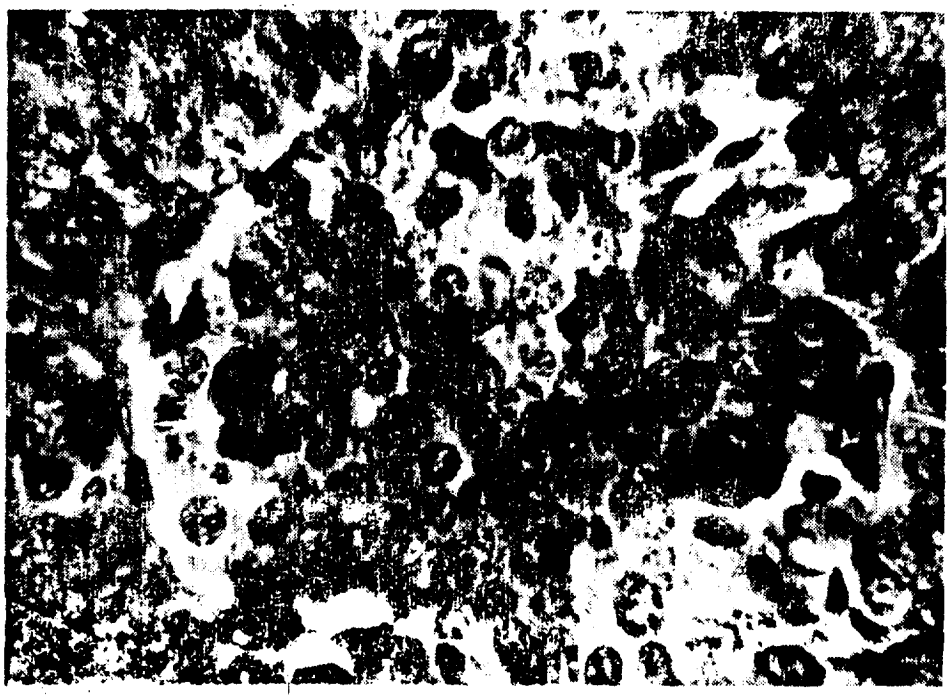

Figure 14. A regular pancreatic islet with several alpha cells (A) of pale appearan ce scattered throughout the islet. Nucl i of beta cells are in sharp contrast to those of giant beta islet cells shown in figures 13 and 15. ×970.

Figure 15. Giant beta islet cells showing prominent negative Golgi images (G). Blood vessel (Bv) in the interstitial connective tissue trabeculae. ×970.