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原　　著

# Changes of A, B and D Cells in Langerhans Islets in Pancreatic Cancers of Hamsters

Noboru Asano, Tadao Manabe, Katsuhiro Imanishi, and Takayoshi Tobe

First Department of Surgery, Faculty of Medicine, Kyoto University
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## Abstract

In order to clarify the effect of pancreatic hormones on the oncogenesis of pancreatic cancer, the kinetics of the B, A and D cells in the islets of Langerhans were studied in hamsters with pancreatic cancer induced by di-iso-propanol nitrosamine (DIPN). Tumors appeared histologically 8 weeks and duct adenocarcinomas became evident 12 weeks after the administration of DIPN. Although the area of the islets did not change in 8 to 16 weeks, the numbers of B cells was decreased 8 weeks after the administration of DIPN and of A and D cells was decreased at 16 weeks.

The area occupied by B cells in proportion to the number of islet cells showed a significant decrease 8 weeks after the administration of DIPN. Since insulin has been reported to have a trophic effect on the exocrine pancreas, our findings suggest that pancreatic B cells start to decrease at the same time that pancreatic cancer begins to form. Thus, insulin appears to play an important role locally in the oncogenesis of pancreatic cancer in acinar cells.

## Introduction

In recent years, the incidence of cancer of the pancreas in Japan has increased greatly, and the number of deaths due to cancer of the pancreas has reached 10,441 deaths in 1986[10].

An apparent association of diabetes and pancreatic cancer has been reported by many investigators[1,4,9,11].

Kessler[12,13] studied cancer mortality in 21,447 diabetic patients registered at the Joslin Clinic in Boston from 1930 to 1956. Among the 15 specific types of cancer examined in this study, a statistically significant excess of deaths was recorded only for pancreatic cancer, in both sexes.

Karmody and Kyle[11] studied patients admitted to the Aberdeen Royal Infirmary from 1955 through 1967 and found that of 265 proven carcinomas of the pancreas during this period, 51 were in

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Present address: First Department of Surgery, Faculty of Medicine, Kyoto University, 54 Shogoin-Kawaracho, Sakyoku, Kyoto 606, Japan.

patients with diabetes. The interval between the diagnosis of diabetes and that of carcinoma was less than 3 months in 25 of the 51 patients, and in only 6 patients was the interval over 2 years.

Thus, diabetes appears to be frequently associated with pancreatic cancer, but it is not known whether pancreatic hormones have any affect on the oncogenesis of pancreatic cancer. In this study, we induced pancreatic cancers in hamsters[17,18,22,23] with di-iso-propanol nitrosamine (DIPN) and followed the kinetics of endocrine cells in Langerhans islets during the development of cancer.

## Materials and Methods

One hundred and twenty five female 8 week-old Syrian golden hamsters weighing 80–100 g (Shizuoka Experimental Animals, Shizuoka) were assigned to a control (n=25) and an experimental group (n=100). The animal were fed a solid diet (Oriental Food, Tokyo) and water ad libitum housed in temperature (23±3°C) regulated animal quarters.

The experimental group received weekly dorsal subcutaneous injections of 500 mg/kg of di-iso-propanol nitrosamine (DIPN, Nakarai Chemicals, Kyoto) for 24 weeks. The control group of hamsters of the same age received the same amount of saline.

Five hamsters in each group were killed 0, 4, 8, 16, and 24 weeks after the start of DIPN or saline injections. The pancreas was removed and fixed with 5% Bouin's solution for 2 hours with 5% formaldehyde for 2 hours. It was cut parallel to the main pancreatic duct through the splenic, duodenal, and gastric lobes of the pancreas[30]. The tissue blocks were dehydrated and embedded in paraffin. Ten serial sections (6 $\mu$m thick) were cut in the central portion of the specimen, transverse to the axis of the pancreas, and stained with hematoxylin-eosin.

The cells in the islets of Langerhans B cells which secrete insulin, A cells which secrete glucagon, and D cells which secrete somatostatin-were stained immunohistologically by the peroxidase antiperoxidase (PAP) method[5] with 3,3-diaminobenzidine as the chromogen in a DAKO PAP kit (DAKO Corporation, Santa Barbara, CA). The sections were preincubated with 10% normal swine serum for 30 min. The serum was suctioned off, and the sections were incubated for 1 hour at room temperature with the primary antiserum, which had been produced in rabbits. The second antibody was swine immunoglobulins to rabbit immunoglobulins, and the PAP-complex was a soluble complex of horseradish peroxidase and rabbit-antihorseradish peroxidase. Endogenous peroxidase was blocked with 1–2% hydrogen peroxidase before exposure to the specific antiserum. The specificity of the immunohistochemical reaction was checked by 1) omission of the primary antiserum, 2) absorption test or incubation in primary antiserum pretreated with excess porcine insulin and glucagon, and 3) control staining of the porcine pancreas. All the specimens were counterstained with Meyer's hematoxylin.

In a randomly chosen slide for each stage, 400 islets in each group were examined microscopically by two blinded observers. The area of islets, the numbers and fractions of each type of endocrine cell among the nucleated cells in an islet, and the area in an islet occupied by each type of endocrine cell were determined. We calculated the the size of the islet, assuming the cut sections of the islets to be elliptical. The areas of the islets were determined by measuring their long and short axes with a square ruled grid (Nikon, Tokyo) in the focal plane of the microscope eye-piece projected onto the islet sections.

Pancreas tumor formation was determined by examining hematoxylin eosin stained sections.

The results of the experiments were evaluated by Student's t-test and analysis of variance

(ANOVA); difference of $p<0.05$ were considered to be significant.

## Results

*Tumor formation in the pancreas.*

No tumor formation was seen 4 weeks after DIPN administration. Tumors appeared in some animals at 8 weeks. Pancreas duct adenocarcinomas became evident at 12 weeks and thereafter. The 63 hamsters which survived for 24 weeks had pancreas tumors. In 27 of them (43%) tumors were macroscopically evident in the duodenal, gastric, and splenic lobes with a slight preference for the head of the pancreas but without any significant difference among the locations. These tumors formed grayish white nodules. The largest tumor was $16\times16\times10$ mm, the smallest $2\times2\times2$ mm. In the remaining 36 animals, the tumors were found under light microscope.

Histologically, all the tumors were adenocarcinomas. Very atypical epithelial neoplastic cells formed disorganized ducts showing the morphology of ductal cell adenocarcinoma (Fig. 1). Tumor cells infiltrated the thickened connective tissue. Papillary proliferations were seen in some cases. Langerhans islets showed no changes for 4 weeks. After 8–16 weeks, dilated neoplastic ducts (so called intrainsular ductal proliferation) were seen within and around Langerhans islets, and these became more prominent later. At 16 weeks Langerhans islets were distorted in the periphery; oval islets became rhombic. At 24 weeks, tumor infiltration caused complete destruction of the islet structure in some animals, and fibrosis of the islets was apparent.

*Area of islets.*

The area of the islets was $1969\pm501$ (mean$\pm$SE) $\mu m^2$ before the administration of DIPN, and $1192\pm278$ $\mu m^2$ at 4 weeks, $1817\pm283$ $\mu m^2$ at 8 weeks, $1332\pm200$ $\mu m^2$ at 16 weeks, and $687\pm175$

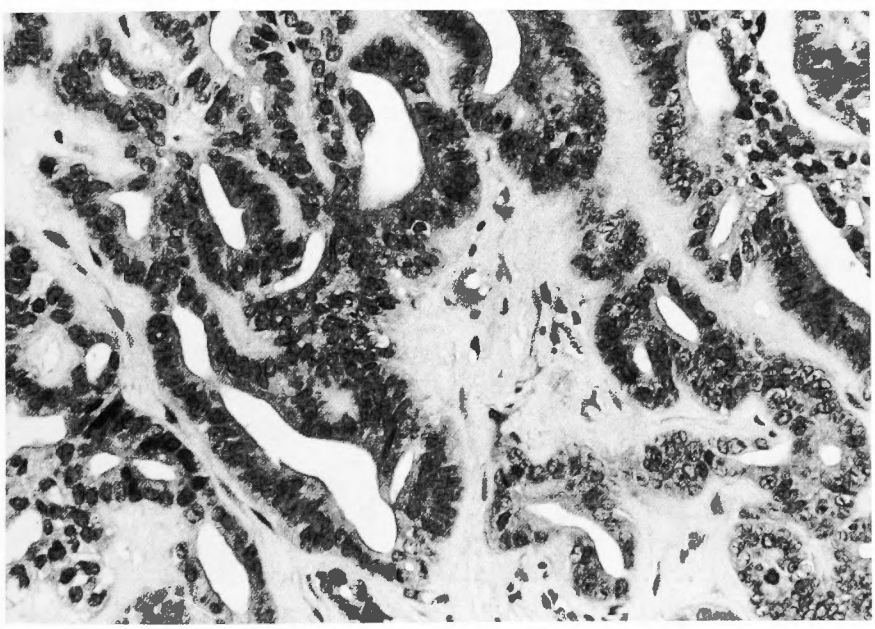


**Fig. 1.** Histological finding of pancreatic carcinoma in hamsters 24 weeks after administration of DIPN. Hematoxylin-eosin staining. ×200.

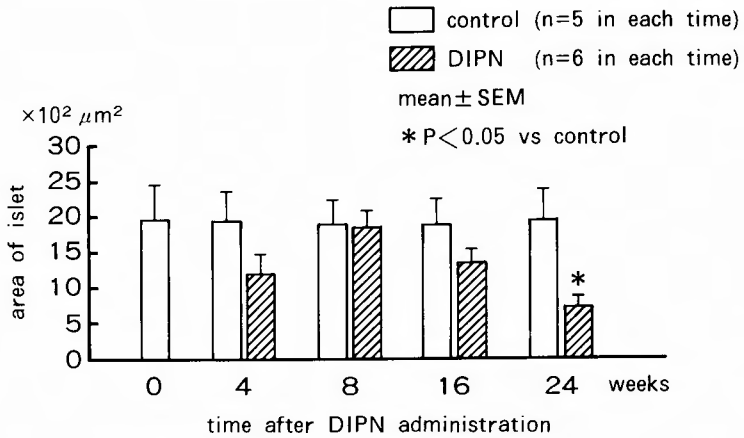
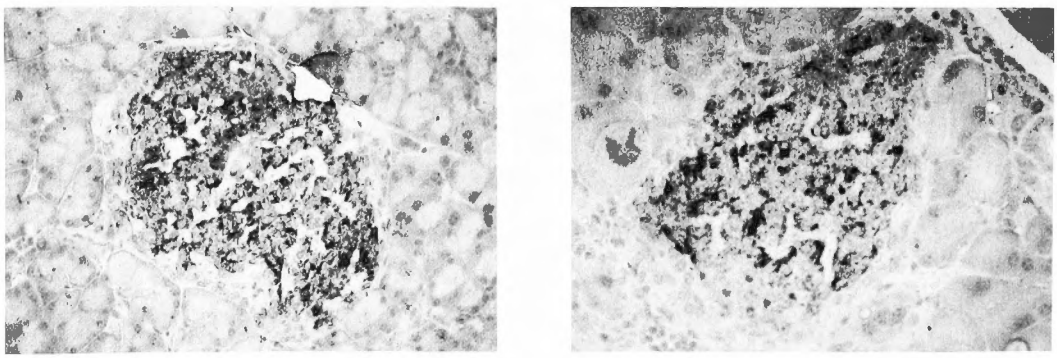



**Fig. 2.** Changes of the area of islets following administration of DIPN in hamster.



a b

**Fig. 3.** Histological findings of B cells in control (a) and at 16 weeks after DIPN administration (b). PAP staining. ×100.

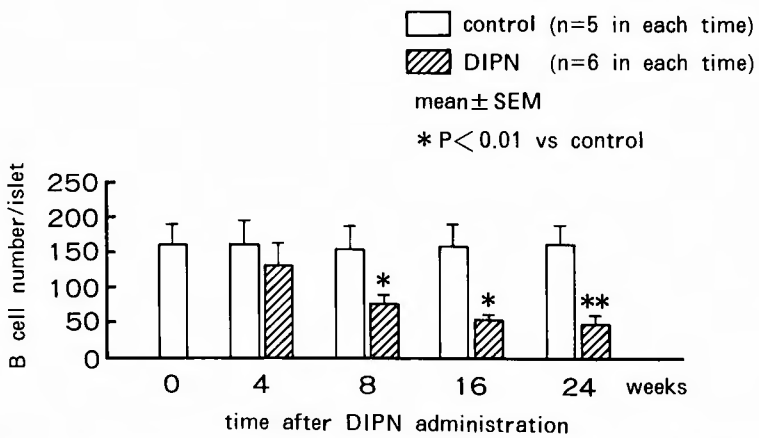



**Fig. 4.** Changes of numbers of B cells following administration of DIPN in hamsters.

$\mu m^2$ at 24 weeks. In the control animals, the area of the islets 4, 8, 16, and 24 weeks after the injection of saline was $1950 \pm 405$ $\mu m^2$, $1890 \pm 385$ $\mu m^2$, $1850 \pm 360$ $\mu m^2$ and $1906 \pm 452$ $\mu m^2$, respectively. The mean islet area at 24 weeks was significantly decreased in the experimental group ($p < 0.05$) (Fig. 2).

The number of insulin producing B cells was $159 \pm 30$ (mean $\pm$ SE) before the administration of DIPN, $130 \pm 36$ at 4 weeks, $78 \pm 9$ at 8 weeks, $56 \pm 6$ at 16 weeks, and $49 \pm 10$ at 24 weeks. In the control animals, the corresponding numbers were $160 \pm 35$, $155 \pm 31$, $158 \pm 29$ and $161 \pm 32$. The numbers at 8, 16, and 24 weeks were significantly different ($p < 0.01$) (Fig. 3, 4).

The numbers of glucagon-producing A cells was $21.6 \pm 3.3$ (mean $\pm$ SE) before the administration of DIPN, $17.7 \pm 1.6$ at 4 weeks, $19.9 \pm 1.4$ at 8 weeks, $7.0 \pm 1.6$ at 16 weeks, and $2.8 \pm 0.9$ at 24 weeks. In the control animals, the corresponding numbers of A cells were $20.5 \pm 3.0$, $19.3 \pm 2.8$, $18.3 \pm 3.2$ and $18.0 \pm 2.9$. The difference between experimental and contral groups was significant at 16 and 24 weeks ($p < 0.01$) (Fig. 5).

The number of somatostatin-producing D cells was $16.8 \pm 2.6$ before the administration of DIPN and $13.8 \pm 1.3$ at 4 weeks, $13.7 \pm 1.4$ at 8 weeks, $9.1 \pm 1.9$ at 16 weeks, and $1.3 \pm 0.4$ at 24

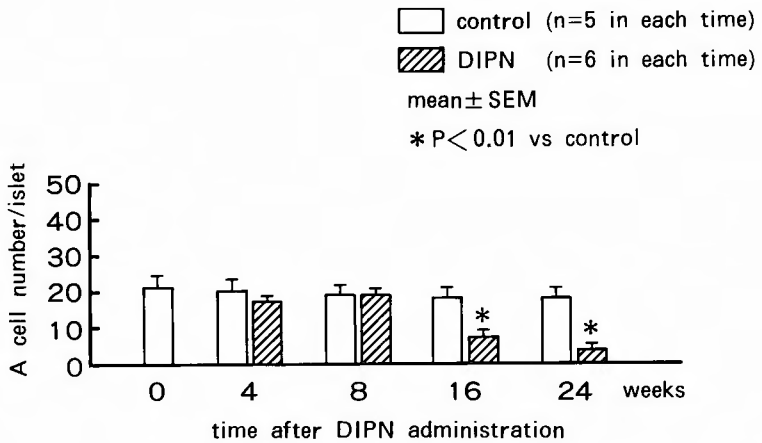
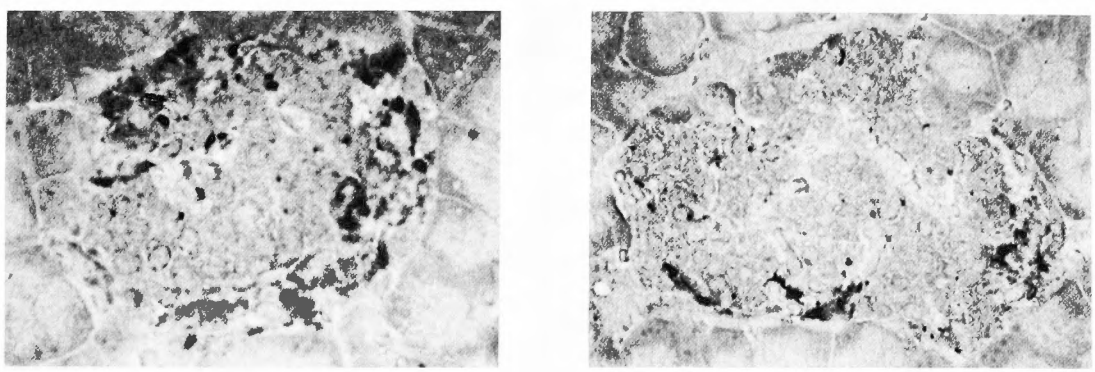



**Fig. 5.** Changes of numbers of A cells following administration of DIPN in hamsters.



a b

**Fig. 6.** Histochemical findings of D cells in controls (a) and 16 weeks after administration of DIPN (b). PAP staining. $\times 100$.

weeks. In the control animals, the numbers were 17.1±2.2, 16.9±2.0, 16.5±1.5 and 15.9±2.1, respectively. The number in the experimental animals was significantly lower at 16 and 24 weeks ($p<0.05$ and $p<0.01$) (Fig. 6, 7).

The proportion of B, A and D cells among the nucleated cells in the Langerhans islets was significantly decreased by the administration of DIPN: B cells from 86.3±3.1% to 75.7±3.5% at 16 weeks ($p<0.05$), A cells from 23.4±1.7% to 12.3±2.2% at 24 weeks ($p<0.01$), and D cells from

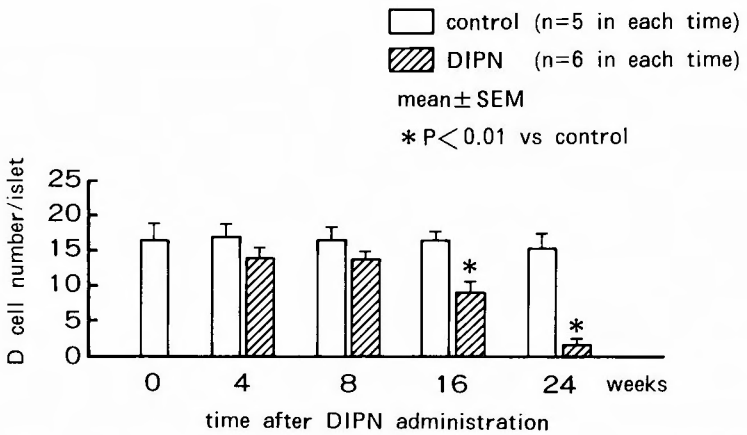



**Fig. 7.** Changes of numbers of D cells following administration of DIPN in hamsters.

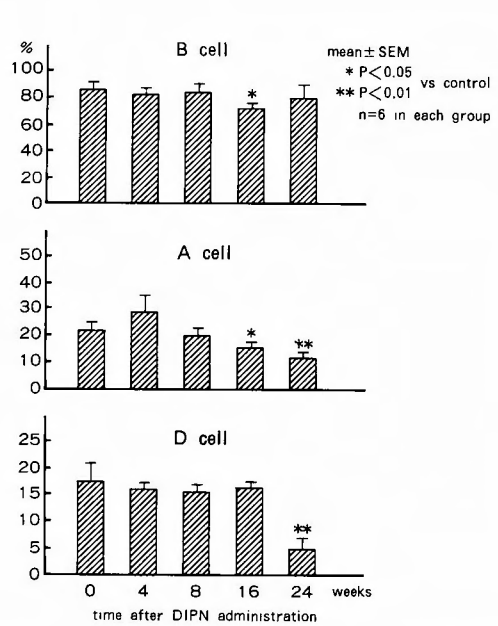



**Fig. 8.** Changes in proportions of B, A and D cells among nucleated cells in the Langerhans islets (endocrine cell number/nucleated cells in Langerhans islets).

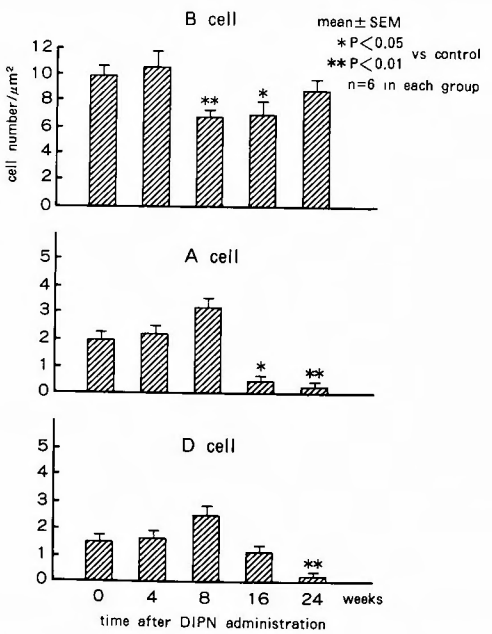



**Fig. 9.** Changes in proportion of B, A and D cells in relation to area of Langerhans islets (endocrine cell number/area of Langerhans islets).

18.0±2.2% to 5.7±1.2% at 24 weeks ($p<0.01$) (Fig. 8).

The number of each type of endocrine cell in relation to the area of Langerhans islets was then analyzed. For B cells, this was 9.8±0.6 pre-administration and showed a significant decrease to 6.1±0.7 at 8 weeks and to 6.4±0.6 at 16 weeks ($p<0.05$, $p<0.01$). For A cells this was 1.9±0.4 pre-administration and 0.5±0.1 at 24 weeks-a significant decrease ($p<0.01$). For D cells, this was 1.5±0.3 pre-administration and decreased significantly to 0.3 to 0.1 at 24 weeks ($p<0.01$) (Fig. 9).

## Discussion

The relationship between pancreas cancer and diabetes has been suspected since an epidemiological study found that patients with diabetes are at a higher than average risk of developing pancreas cancer[1,4,8,9,11,32]. It has also been reported that prediabetic patients have a higher risk of pancreas cancer[12,13]. However, some controversy remains since there are claims that diabetes may be a secondary change caused by the inflammation accompanying pancreas cancers. We used DIPN to induce pancreas cancers in hamsters. The experimental pancreatic cancer due to nitroso-compounds closely resembled human pancreas cancer[17–25]. We followed the kinetics of endocrine function during the oncogenesis of pancreas cancer. The pancreas cancers induced in hamsters by the N-nitroso-compound were ductal adenocarcinomas with some papillary proliferation. They metastasized to lymph nodes and liver and were disseminated to the peritoneal cavity and finally killed the animals. DIPN caused only occasional cholecystic duct tumors and seldom caused tumors in other sites in the digestive system. Thus, N-nitroso-compound-induced pancreas cancers are an ideal model for the study of pancreas cancers.

In the present study we describe the kinetics, the number of cells, and the area occupied by three types of endocrine cells in the pancreas: B, A, and D cells. B cells decreased 8 weeks and A and D cells 16 weeks after DIPN administration. In the experimental model described here, animals developed tumors of the pancreas within 8 weeks and pancreatic duct carcinomas 12 weeks after the administration of DIPN; thus, pancreatic acinar cells were probably affected by 8 weeks. These results indicate that pancreatic endocrine B cells started to decrease at the same time that the formation of pancreas tumors started with changes in the pancreatic duct epithelium or pancreatic acinar cells.

Insulin has been known to have local tumor-promoting effects by accelerating DNA synthesis on its own or in cooperation with other factors, acting like a growth hormone[28]. In regard to the relationship between diabetes and pancreatic oncogenesis, it has been reported that the subcutaneous injection of nitrosobis (2-oxopropyl) amine (BOP), does not induce cancer in genetically diabetic Chinese hamsters but can induce ductal adenocarcinoma in non-diabetic EP hamsters[2]. Bell et al[3] reported that the intraperitoneal injection of streptozotocin (STZ), a B-cell toxin, prevented the induction of tumor by BOP in hamsters. Pour's group has reported[6,21,24] a similar effect of STZ in a system using N-nitroso (2-hydroxypropyl) (2-oxopropyl) amine (HPOP), a derivative of B-ketonitrosamine which is an analogue of BOP Pour et al[6,21,24] suggested that the Langerhans islets play an important role in the oncogenesis induced by nitrosamines like BOP and that the cyclic form of HPOP has a glycosidic residue similar to that of STZ and is efficiently taken up by islet cells where it is converted to N-nitrosomethyl (2-oxopropyl) amine (MOP) which may stimulate the pancreatic cells via post-incular capillaries. Thus, the Langerhans islets may be involved in the oncogenesis of acinar cells through the metabolism of carcinogens. Insulin causes exocrine pancreatic hyperplasia

and has been shown to increase secretion into pancreatic ducts.

Anatomically, most of the blood supply to the pancreas flows through the Langerhans islets. The trophic effect of insulin on pancreatic acinar cells is caused by its binding to acinar cells followed by internalization and stimulation of protein synthesis within the acinar cells[7,14,27,28]. Histologically, acinar cells immediately surrounding the pancreatic islets appear to be most sensitive to the trophic effect of insulin[14,15,26]. In the normal pancreas, the acinar cells close to the Langerhans islets are in a halo configuration[15].

Since periinsular exocrine cells seem to be sensitive to nitrosamine-induced carcinogenesis[25], when nitrosoamines are present, they have an additive effect to the trophic effect of the pancreas hormones, promoting oncogenesis. Our experiments showed that B cells decreased during the initiation phase prior to the start of tumor formation. This indicates that B cells are damaged by the carcinogen and therefore that insulin is internalized during carcinogenesis. This is also suggested by the slower decrease of A and D cells than of B cells.

Somatostatin is a hormone which is widely distributed in the nervous and digestive systems. It plays an important role in homeostasis by inhibiting the release of growth hormone, gastric acid, gastrin secretion, and insulin secretion. In the present experiment the number of D cells and their proportion among the nucleated cells in the Langerhans islets was decreased 16 weeks after DIPN administration, and the ratio of the area occupied by D cells was also decreased. Szende[29] and Paz-Bouza[16] have reported that D-Phe-Cys-Try-D-Try-Lys-Val-Cys-Try-NHZ (RC-160), an analogue of somatostatin, together with luteinizing hormone-releasing hormone ((D-Try6) LH-RH) decreased the rate of tumor formation by BOP and prolonged the survival of the animals that received these drugs in comparison with animals that received BOP only. Although this does not provide the mechanism of the decrease of D cells in our experiment, it may have promoted oncogenesis.

The area of Langerhans islets did not change significantly soon after DIPN administration, but in 24 weeks and thereafter, it decreased.

Histological examination showed intrainsular ductal proliferatiion 8 weeks after DIPN administration. In 16 weeks, Langerhans islets changed from oval to rhomboid. The size of Langerhans islets generally does not differ according to species, sex, or age. Takahashi and Pour[31] measured the long axes of 100 Langerhans islets in hamsters 18, 57, and 123 weeks of age to follow the kinetics of Langerhans islets. The percentage of islets measuring 50 $\mu$m or less was 6, 10, and 9% in 18, 57, and 123-week-old hamsters, respectively. Islets measuring 50–300 $\mu$m were seen in 89, 90 and 82%, respectively. They suggested that the size of Langerhans islets does not change significantly with age and found intra-insular ductal proliferation in 5% of male hamsters, but its incidence was not correlated with age. This suggests that the decrease in the are of Langerhans islets 24 weeks after DIPN administration is not due to aging but is caused by the decrease of B, A, and D cells which was apparent at 8–16 weeks, the progression of pancreas cancer, and the fibrosis of the pancreas which accompanies cancer. The appearance of intrainsular ductal proliferation suggests that the changes in the acinar cells, especially the peri-insular acinar cells and in the Langerhans islets appear early although to what extent the drug has directly contributed remains to be known.

In this study, we cannot determine a relationship between diabetes in elderly persons and pancreatic cancer. Adult onset diabetes is a complex disease, characterized by inadequate insulin production and impaired insulin response. Further study is necessary to elucidate the endocrine abnormalities associated with pancreatic cancer in humans. Our present study may stimulate further investigation of the relationship between endocrine secretion and exocrine pancreatic carcinogenesis in

hamsters.

**Acknowledgment**

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## 和文抄録

# ハムスター膵癌におけるランゲルハンス氏島のA, B, D 細胞の変化

京都大学医学部第1外科学教室
浅野 昇，真辺 忠夫，今西 勝大，戸部 隆吉

膵癌の発生過程における膵内分泌ホルモンの影響をみる目的でDi-iso-propanol nitrosamine (DIPN) 誘発ハムスター実験膵癌を用い，経時的に膵ランゲルハンス氏島の面積，B, A, D 細胞の変化を観察した．

その結果，DIPN 投与後，8週後より腫瘍の発生がみとめられ，24週までに生存しえた実験動物すべてに管状腺癌を主とする腺癌が認められた．ラ氏島の面積は DIPN 投与16週後まで有意な変化を示さなかったが，24週には有意に縮小した．B 細胞数は8週より減少し，A, D 細胞はともに16週より減少がみられた．ラ島内有核細胞数に対する内分泌細胞構成比は，B, A 細胞は16週，A, D 細胞は24週に低下し，ラ氏島面積に対する内分泌細胞構成比では，B 細胞は8，16週，A 細胞は16週，D 細胞は24週に低下がみられた．

このように膵癌発生時期に一致して，B 細胞が減少し，その後，A, D 細胞が減少することより膵腺房細胞の局所における膵癌の発癌過程にインスリンが何らかの作用を持っている可能性が示唆された．