SCIENTIFIC REPORTS

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ERRATA

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33	28	K. Okabe	H. Okabe
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57	11	evolutinary	evolutionary
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90–91	Photo legends	Roentgenogram showing giant rugae of the gastric mucosa. Endoscopic piture of giant rugae of the gastric mucosa.	Endoscopic picture of giant rugae of the gastric mucosa. Roetgenogram showing giant rugae of the gastric mucosa.
97	4	sharaply	sharply
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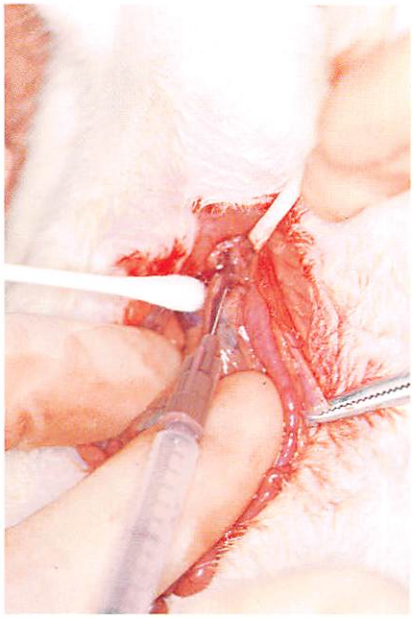
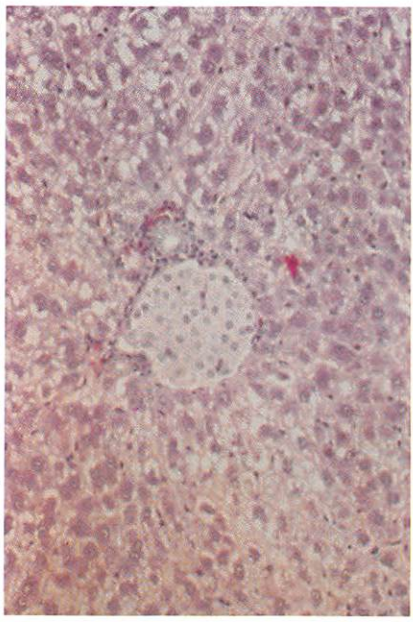
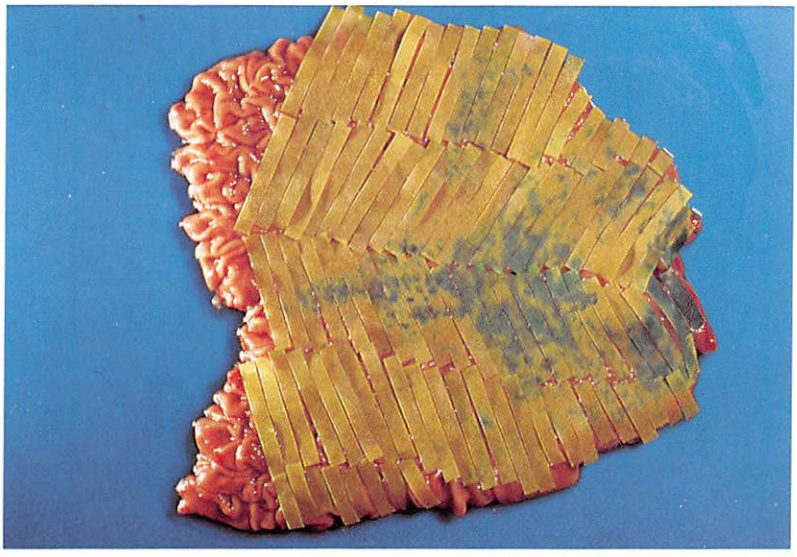
Surgery



Transplantation of Langerhans' islets via portal vein



Liver 48 hours after transplantation. An embolic pattern of L's islets in the portal vein of the portal space -Glisson's sheath was observed.



Intestinal metaplasia in the gastric mucosa by detection of disaccharidases with Tes-Tape

DEPARTMENT OF SURGERY

GENERAL SUMMARY

The Department of Surgery was set up additionally in the Cancer Research Institute on April 18, 1977.

Today, it is generally known that resecting cancerous lesion surgically is the most effective method in the treatment of cancer.

The work of the Department of Surgery, specializing in cancer of the digestive organs, is directed toward experimental and clinical studies on the pathogenesis, differentiation, proliferation and metastasis of cancer and also toward the development of surgical treatment of malignant tumors. At the same time, it is going ahead with the clinical application of analysis of elementary reactions obtained in the fundamental studies and results of studies on the carcinostatic and diagnostic methods.

Studies are under way on five subjects as follows:

1. **Clinical studies on immunotherapy for cancer.**
   The existence of antigen showing specificity to cancerous cells is demonstrated rather accurately. How to increase the weak antigenicity has become an important problem facing treatment by immunotherapy. The Department of Surgery in cooperation with the department of fundamental study measures the cellular function or the immune response of the cell by administering drugs before and after surgery, and particularly examines the therapeutic results of nonspecific immunotherapies.
2. **Clinical studies in relation to diagnosis of cancer.**
   Studies on the results of mass examination of the stomach and studies aiming at improving the rate of early diagnosis of gastric cancer.
3. **Fundamental studies on lymphatic chemotherapeutics for cancer.**
4. **Fundamental and clinical studies in relation to chemotherapies for cancer.**
   Particularly, examination of various methods of administration based on the determination of concentrations of carcinostatic drugs in tumor and lymph node.
5. **Transplantation Surgery.**
   Studies on transplantation for functional/metabolic disturbance of organs arising from surgical treatment of cancer.

These studies were supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan, and by a Grant-in-Aid for Cancer Research from the Ministry of Education, Science and Culture, Japan.

ABSTRACT

(55) Morphological observations on and viability of frozen isolated rat pancreatic L islets

G. Nakagawara, S. Ohno, T. Mizukami, M. Mai, R. Akimoto, T. Mura, and K. Kitagawa

Today when total pancreatectomy (an expanded surgery aimed at radical treatment) can be performed positively and safely for cancer of the pancreas, cases of which have tended to increase in number in recent years, the necessity of transplantation aimed at making up for the endocrine defect after total pancreatectomy is keenly being felt.

Based on the idea that transplantation of preserved L isletes is preferable from the viewpoint of securing "donor islet" in order to make studies on pancreatic L islets develop in a more realistic and more clinical direction, we have conducted experiments to preserve pancreatic L islets by a method making use of organ incubation. We have clearly demonstrated by *in vitro* experiments that the preserved L islets possess insulin releasing activity

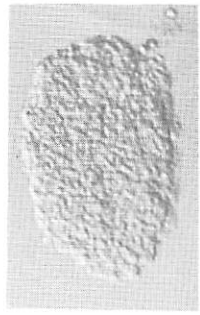


Fig. 1. Fresh islet were seen as an islet with a clearcut boundary (differential interference microscope -X84).

Fig. 2. Isolated L islet after thawing in Group III showed marginal unevenness and presented a picture most similar to the control (differential interference microscope - X84).

equal to that of fresh L islets functionally till the seventh day of preservation[1].

In the present experiment, we have performed cryopreservation for organ preservation, made morphological observations on frozen isolated rat pancreatic L islets for 7 to 10 days and further conducted studies on their viability, and have reached the following conclusions:

1. Group III (cryopreserved as isolated L islets) had less structural destruction, showed a picture similar to the control, and could be cryopreserved for 7 to 10 days. (Fig. 1, Fig. 2)
2. (−196°C) 20% DMSO, (−196°C) 10% DMSO and (−80°C) 20% DMSO in this order maintained the insulin releasing activity well and had biological function, the ratio to the control being 51.3%, 50.0% and 43.7%.
3. Group III (cryopreserved as isolated L islets) maintained about 50.0% of the insulin releasing activity *in vitro*; thus, it is expected we will demonstrate viability even *in vivo*.

1) Nakagawara, G. et al., Surgery, **83**, 188 (1978).

(56) Preserved pancreatic islets transplantation in diabetic rats.

G. Nakagawara, S. Ohno, T. Mizukami, M. Mai,
R. Akimoto, T. Mura and K. Kitagawa

The rate of death due to diabetic coma has decreased sharaply since insulin was discovered by Banting and Best in 1922[1]. As the life span of diabetics is prolonged and duration of illness becomes longer, it has become inevitable for diseases of small blood vessels, particularly diabetic nephrosis and retinopathy to develop; and establishing a method for prevention and treatment of these diseases is urgently called for.

Pancreas transplantation, once forsaken after the discovery of insulin, has come to be studied more actively from various angles to see if pancreas transplantation is effective in preventing diabetic nephrosis from advancing.

Pancreas transplantation by vascular anastomosis and transplantation of Langerhans' islets are being tried as the method for pancreas transplantation. Many researchers have been exercising their ingenuity on pancreas transplantation using whole organ by vascular anastomosis since Lichtenstein[2] rendered a report on it. However, transplantation using the whole organ failed to attain its objective. And the coexistence of extrapancreatic secretory cells was said to be responsible for the failure.

Meanwhile, efforts of researchers centering around Lacy[3] have made it technically easy to obtain pancreatic islets.

Ballinger-Lacy[4] performed a homotransplantation of 400–600 islets into the abdominal cavity of rats with experimental diabetes, reporting that diabetic rats with persisting hyperglycemia showed improvement in diabetic conditions.

If this transplantation of pancreatic islets is to be developed in a more realistic and clinical direction, transplantation of preserved pancreatic islets is preferable partly for the sake of securing a supply of "donor islet".

Thus, we preserved pancreatic islets by a method making use of organ cultivation and made it clear by *in vitro* experiments that pancreatic islets preserved have insulin releasing activity equal to that of fresh pancreatic islets up to the 7th day of preservation[5].

Rat pacreatic islets were preserved for 3 to 5 days by a method making use of organ cultivation.

In order to study the possibility of transplanting these preserved pancreatic islets, we implanted 250–300 islets into the portal vein of streptozotocin induced diabetic rats to reach a conclusion as follows.

1. By injection of preserved pancreatic islets into the portal vein, the diabetic conditions of streptozotocin induced rat were improved markedly within about one week after transplantation; blood glucose decreased to around 100 mg/dl, urine glucose to 0.5 g/day or less and its effectiveness lasted 16 weeks. (Fig. 1).
2. On the glucose tolerance tests, blood glucose and blood IRI after addi-

tion changed almost correspondingly, showing the highest values five minutes after addition, and tended to decrease gradually thereafter in the transplanted group. Glucose tolerance and insulin releasing reserve activity were also improved markedly.

3. The transplanted group showed good IRI reacticity to added tolubutamide or glucagon. From the above results it was surmised that preserved pancreatic islets demonstrated its function fully even after injection into the portal vein and was effective for improving diabetic conditions.

1) Banting, F. G. and Best, C. H., Canad. Med. Ass. J., 12, 141 (1922).
2) Lichtenstein, I. L. and Barshar, R. M., J. Internat. Coll, Surg., 28, 1 (1957).
3) Lacy, P. E. and Kastinovsy, M., Diabetes, 16, 35 (1967).
4) Ballinger, W. F. and Lacy, P. E., Surg., 72, 175 (1972).
5) Nakagawara, G. et al., Surg., 83, 188 (1978).

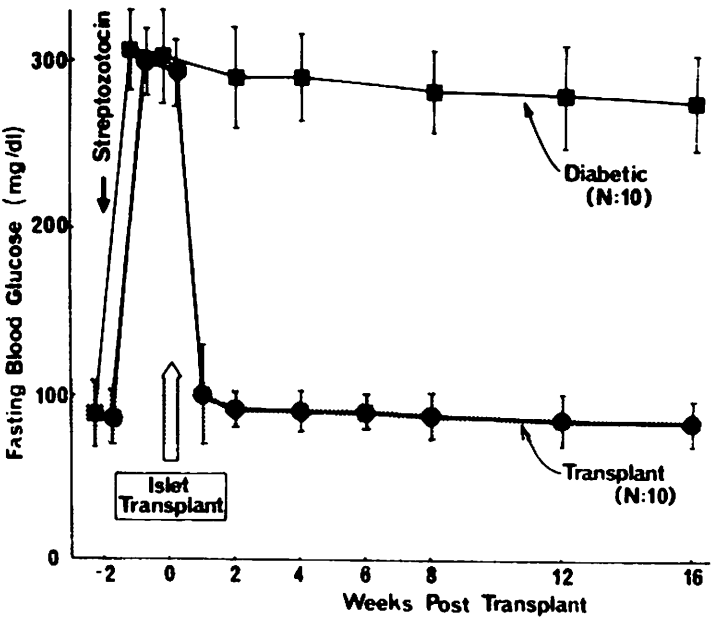


Fig. 1. Changes in blood glucose after transplantation of preserved L's islets. Each value is of mean ± S.D. n=10

(57) On the viability of L islet of perfused pancreas of rat cadaver.

G. Nakagawara, S. Ohno, T. Mizukami, M. Mai,
R. Akimoto, T. Mura and K. Kitagawa

The life span of diabetics has been prolonged and duration of illness has become longer since insulin was discovered. Consequently, occurrence of diseases of small blood vessels, particularly diabetic nephrosis and retinopathy has become inevitable, and establishment of the method for prevention and treatment of these diseases is being urged.

Ever since transplantation of the pancreas was found to be effective for preventing diabetic nephrosis from advancing, studies on transplantation of the pancreas have become active.

Thinking that transplantation of preserved L islet is preferable in order to bring transplantation of pancreatic L islet to a more practical and clinical level and also to secure "donor islet", we preserved pancreatic L islet by a method making use of organ cultivation and made it clear by *in vitro* experiments that preserved L islet functionally maintains the insulin secretory activity about equal to that of fresh L islet up to the seventh day of preservation.

In the present study, with respect to the use of the pancreas of the cadaver, we examined experimentally methods of preserving by perfusion and post-perfusion viability of pancreatic L islet of the rat cadaver to obtain some findings (Fig. 1). The conclusions are reported here.

1. The low temperature perfusion of the pancreas is possible up to five hours.
2. The number of L islets isolated by the collagenase treatment decreased with the lapse of time.
3. The Pancreozymin-added group cannot maintain the insulin releasing activity over so many hours compared with the non-added group.
4. The ischemia permissible time for the pancreas in the room temperature group lies somewhere between two and three hours from a histological viewpoint.

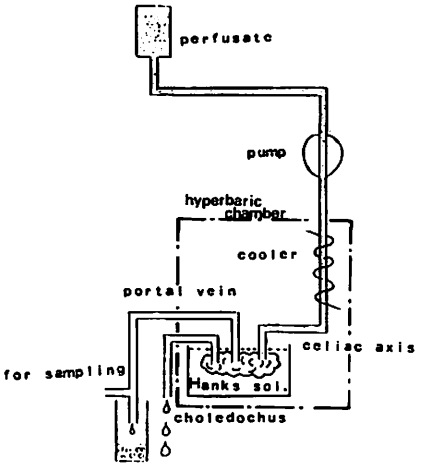


Fig. 1. The schema of the perfusion apparatus.

(58) A histological study of colonic and rectal polyp and its relation to early cancer.

R. Akimoto, G. Nakagawara, M. Mai, S. Ohno, T. Mura, T. Mizukami and I. Kitagawa

The malignant potential of adenomas of the colon and rectum varies with size, histological type and grade of epithelial atypia. A review of all patients with a histological diagnosis of colonic and rectal polyp from 1975–78 at our Institute was undertaken. We have experienced 39 lesions of colonic and rectal polyps in the 30 patients, including 15 cases polypectomized endoscopically or at surgery, and 6 cases co-existing with frank carcinoma of colon and rectum. There were 17 pedunculated, 19 subpedunculated, and 3 flat polyps; 87.2 per cent were in the left colon, 7.7 per cent in the transverse colon, and 5.1 per cent in the right colon. Among these polyps 34 lesions were adenomas and 4 metaplastic polyps. All the adenomas were histologically graded into four degrees of epithelial atypia according to cytological criteria[1]. One case was Peutz-Jeghers type polyp with focal atypia. All of the adenomas beyond 15 mm in diameter showed severe dysplasia (carcinoma *in situ*, focal cancer) and invasive cancer. Two adenomas with carcinoma *in situ* were under 10 mm at the largest diameter. All malignant polyps were situated in the sigmoid colon and rectum. Malignant transformation rate of adenoma in this series encountered 35.5 per cent, excluding invasive cancer without benign adenomatous tissue in tumor (Table).

As a conclusion, frank cancer was very often associated with multiple adenomas, and two lesions of malignant polyp were under 10 mm in diameter, so that it was suggested that the greater number of carcinomas might have arisen from adenoma.

1) Muto, T. et al., Cancer, **36**, 2251–2270 (1975).

Table. Histological study of colonic and rectal polyps.

Size (mm)	Metaplastic Polyp	Histological Grade of Adenoma					Total
		Grade 1	Grade 2	Grade 3	Grade 4	Invasive Cancer	
Under 5	● ●	● ● ●	● ● ● ● ●	●	●		12
6 – 10	● ●	● ●		▬ ● ● ● ●	●		10
11 – 15			● ● ●	●	● ● ●	▬ ▬	9
16 – 20					● ●		2
Over 21	●*				● ● ● ●	●	6
Total	5**	5 (14.7%)	8 (23.5%)	7 (20.6%)	11 (32.4%)	3 (8.8%)	39 lesions
		34 lesions					

● Pedunculated, ● Sub-pedunculated, ▬ Flat.
* P-J polyp with focal adenoma.
** One case was focal atypia.

(59) Intestinal metaplasia of the gastric mucosa; a histological study of its distribution in early gastric carcinoma.

M. Mai, G. Nakagawara, R. Akimoto and I. Kitagawa

Intestinal metaplasia is one of the most important histological changes appearing in the gastric mucosa of various diseases. Particularly, intestinal metaplasia is well known to be closely related to highly differentiated adenocarcinoma of the stomach. In this paper the degree and the extent of intestinal metaplasia in the stomach with carcinoma and atypical epithelium were studied.

The stomach materials resected for 49 early gastric carcinomas were obtained from June of 1975 to September of 1978 at the Cancer Institute Hospital of Kanazawa University. Serial strips of 5mm thickness parallel to the lesser curvature of the whole stomach were taken for microscopical investigation, and as many as 60 blocks were obtained from one stomach. The specimens were sketched in order to visualize the stereoscopic relations between intestinal metaplasia and carcinomatous lesion. Metaplastic sites were plotted on this map together with the extent of carcinomatous lesion. The patterns of the extent of the metaplastic process were classified into A) pyloric type, B) transitional type extended up to pyloric-fundic border, C) discretely extensive type, D) diffusely extensive type and E) fundic diffuse type. Regarding histologic types, carcinomas were divided into two types; a) highly differentiated adenocarcinoma (tubular and papillo-tubular adenocarcinoma) and b) undifferentiated adenocarcinoma (signet ring cell carcinoma and anaplastic carcinoma).

As shown in Table, highly differentiated carcinomas showed 61.7% of diffuse type and there was only one case which totally failed to show intestinal metaplasia in stomach for all areas examined. On the other hand, metaplastic changes of undifferentiated carcinomas were slight, and there were five cases (35.7%) of non-metaplastic type in this group. It is suggested that no distinct correlation between undifferentiated carcinomas and the extent of intestinal metaplasia can be noted. The incidence of metaplasia close to carcinomatous lesion was investigated in 71 lesions in 49 cases with early gastric carcinomas. Fairly profuse metaplasias were present in 92% of highly differentiated adenocarcinomas. The remaining 8% failed to show metaplastic changes in the neighbourhood, but these were accompanied instead by pyloric gland hyperplasia. Metaplasia in undifferentiated carcinomas was absent in 53.9%. Furthermore, we analysed metaplastic changes in cases with multiple simultaneous carcinomas in stomach which yielded extremely good conditions for such studies and much favourable material. The incidence rates of diffuse type were 45% in single carcinomas and 69.2% in multiple carcinomas, all of which revealed highly differentiated adenocarcinomas. It is therefore noteworthy that multicentric carcinomas showed high incidence in diffusely intestinized mucosa of highly differentiated carcinomas.

Table. Comprtative spots of metaplastic changes in early gastric carcinomas and atypical epithelium.

patterns of intestinal metaplasia \ histological types	a) highly differentiated adenocarcinoma		b) undifferentiated adenocarcinoma		a) + b)	atypical epithelium associated with carcinoma	total
	single	multiple	single	multiple	multiple		
non-metaplastic	● 1 (2.9%)		● 5 (35.7%)			● 1	6 cases
intestinal metaplasia A) pyloric type	0 (0 %)		● 1 (7.1%)				1 case
intestinal metaplasia B) transitional type	●● 2 (5.9%)		●●●● 4 (28.6%)			●● 2	6 cases
intestinal metaplasia C) discretely extensive type	●●●●● ●● 10 (29.4%)	●●●	●● 3 (21.4%)	●		● 1	13 cases
intestinal metaplasia D) diffusely extensive type	●●●●● ●●●● 18 (52.9%)	●●●●● ●●●●	● 1 (7.1%)			●●●●● ●●●● 9	19 cases
intestinal metaplasia E) fundic diffuse type	● 3 (8.8%)	●●	0 (0 %)		● 1	● 1	4 cases
total	20	14	12	2			
	34 cases (100%)		14 cases (100%)		1 case	14 cases	49 cases

Atypical epithelial lesions were often found in stomach, most of which co-existed with frank carcinomas in the same stomach. In this series 14 cases (28.6%) were associated with atypical epithelium, and these atypical lesions associated with severe intestinized mucosa were present in 47.6% of highly differentiated adenocarcinoma. Morphological studies of highly differentiated carcinomas and their associations with atypical epithelium have been of our main interests, but it is beyond the limit of this survey to report our work in detail in this paper.

Turning to the subject of gastric carcinomas and their relation to intestinal metaplasia, these leave no doubt that the metaplastic process is more severe in stomach with highly differentiated carcinoma than in that with undifferentiated carcinoma, and that the prevalence of intestinal metaplasia might be used as an indicator of gastric cancer risk. This does not, however, mean that highly differentiated carcinomas in all cases arise from intestinal metaplasia. We are not able to decide without further histological investigations whether or not most of these highly differentiated carcinomas originate from intestinized mucosa as precancerous condition. Experimental studies on carcinogenesis in animals may possibly help to elucidate this gap in our knowledge.

1) Morson, B. C., Brit. J. Cancer, 9, 377–385 (1955).
2) Johansen A. A., Current Topics in Pathology edited by B. C. Morson. (I) Early gastric cancer. 1–14p, Springer-Verlag Berlin Heidelberg New York, (1976).
3) Nakamura K. et al., GANN, 59, 251–258 (1968).