THE EFFECT OF PANCREATIC DUCT LIGATION ON THE GASTRIC INHIBITORY

POLYPEPTIDE (GIP), GASTRIC ACID SECRETION AND GLUCOSE METABOLISM IN DOGS

BY

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ABSTRACT

(A)  Gastric Secretion

The present study was performed to investigate the canine post-pancreatic duct ligation GIP secretion in response to fat ingestion using a meat meal mixed with unhydrolyzed or hydrolyzed whipping cream, and to determine whether GIP plays a role in the production of hyperacid secretion in the pancreatic duct ligated dogs.

Four mongrel female dogs were prepared with Heidenhain pouch (HP) and gastric fistula (GF), and daily acid secretion from the HP was measured before and after pancreatic duct ligation (PDL).  HP acid output, serum immunoreactive gastrin (IR-Ga) and serum immunoreactive gastric inhibitory polypeptide (IR-GIP) concentrations during five hours following oral ingestion of a meat meal alone, a meat meal mixed with 125g of unhydrolyzed cream and meat meal mixed with 125g of hydrolyzed cream were measured before and after PDL.

Twenty four hour HP acid outputs increased significantly in each of the four dogs after PDL.  Five hour HP acid outputs in response to a meat meal alone and a meat meal plus unhydrolyzed cream were modestly increased, while those in response to a meat meal plus hydrolyzed cream were rather reduced after PDL.  Serum IR-Ga responses to all stimulants were lowered after PDL and those to meat meal plus hydrolyzed cream lowered most markedly.

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Serum IR-GIP responses to a meat meal alone were significantly increased, while those to a meat meal plus unhydrolyzed and hydrolyzed cream were reduced.

The results of the present study demonstrate serum IR-GIP in response to a meat meal is increased by PDL in dogs, suggesting augmented acid juice passing into the intestinal lumen is responsible for the increased GIP response. It is indicated that hypo-secretion of GIP is not the cause of hypersecretion of gastric acid in the PDL dogs.

(B) Glucose Metabolism.

Functional alteration in glucose homeostasis especially concerning the early onset of diabetes after PDL was studied in dogs. Intravenous (i.v.) and intragastric glucose tolerance tests were performed at two to ten weeks and two weeks after PDL respectively. Serum glucose, IRI, and IR-GIP in response to a meat meal with and without unhydrolyzed or hydrolyzed fat were estimated at six weeks after PDL.

Significantly impaired glucose tolerance and early phase IRI secretion after i.v. glucose were shown at two to ten weeks after PDL. Intragastric glucose load revealed delayed pattern of serum glucose and IRI (no evidence of glucose intolerance or diminished IRI secretion), indicating decreased gastric motility after PDL. Serum IR-GIP response to intragastric glucose load was not attenuated by the operation but showed a similar pattern to IRI response. Serum IRI responses to meat meals with and without unhydrolyzed or hydrolyzed cream were impaired after PDL.

It is indicated that[1] dogs after PDL show early onset (two to ten weeks) of diabetes, i.e. blunted early phase insulin secretion,[2] the mechanism of GIP secretion as an insulinotropic enterohormone remains intact after PDL if sufficient stimulants are given.

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INTRODUCTION

Canine gastric hypersecretion following PDL is a well-known phenomenon,[1,2,3,4] but the mechanism(s) for this phenomenon remains obscure. It is generally accepted that the gastric hypersecretion may be due in part to the absence of by-products of fat digestion which normally stimulate release of gastric inhibitory hormone(s) from the duodenum and small bowel.[5] Feng et al[6] demonstrated that duodenal irrigation by fat suppressed the acid secretion of transplanted gastric pouches, indicating that the inhibition was humorally mediated, and Kosaka and Lim[7] proposed the name "enterogastrone" for the humoral inhibitory agent. GIP has been found to satisfy the criteria as an enterogastrone in dogs,[8] but in innervated stomach preparations of the dog[9] and in normal man[10] inhibition of pentagastrin stimulated acid secretion by GIP was found to be weak.

It has been speculated that a disturbed GIP release may be responsible for the abnormal acid secretion in duodenal ulcer disease. Contrary to this assumption, an exaggerated GIP release following oral glucose or test meal was observed in patients with duodenal ulcer.[11,12] GIP is known to potentiate glucose induced insulin release, and the increase in blood levels of glucose and GIP in the majority of duodenal ulcer patients, leading to an increased insulin response, might be explained by an enhanced absorption of glucose by the small bowel mucosa, possibly as a consequence of an abnormally rapid rate of gastric emptying and/or increased intestinal motility[13].

Ebert et al[14] demonstrated intraduodenal infusion of hydrochloric acid (HCl) dose dependently potentiates glucose induced insulin release in rats, while Brown et al[15] failed to show IR-GIP release in dogs by HCl. Recently, LeRoith et al[16] showed that HCl by itself is capable of stimulating GIP in man, suggesting physiological significance of acid induced GIP secretion.

Functional alteration in glucose metabolism as well as gastric acid secretion is an important physiological problem in human and animal performed PDL. It is well known that PDL results in atrophy and fibrosis of the exocrine pancreatic tissue. Detailed morphological studies[17] at various intervals after PDL in rats have revealed that acinar cells completely disappear within one week and never reappear, and PDL caused some initial damage to the islet with subsequent regeneration of the islet parenchyma. Whether the endocrine function will finally deteriorate after PDL or not has so far been controversial. Heptner et al[18] observed that four to six months after PDL in dogs both the intragastric and the i.v. glucose tolerance were impaired and the increase in serum IRI was diminished after intragastric and i.v. glucose load, indicating the abnormality in glucose tolerance as a consequence of islet cell damage after PDL.

## PURPOSE OF STUDY

The purpose of the present study is to investigate the canine post-PDL GIP secretion in response to fat ingestion using a meat meal mixed with unhydrolyzed or hydrolzyed cream, and to determine whether GIP plays a role in the production of hyperacid secretion in the PDL dogs. The present study was also designed to obtain further information about earlier changes of glucose tolerance after PDL in dogs.

MATERIALS AND METHODS

Four healthy mongrel dogs, initially weighing between 15 and 20 kg were used. They were prepared with Heidenhain pouch (HP) and gastric fistula (GF). The GF was made in the most dependent portion of the stomach. Stainless steel canulas were used for the HP and GF. After allowing three weeks for recovery, the first series of tests was started as control study.

1.    Twenty Four Hour Acid Study.

Twenty four hour gastric secretion was collected daily in a glass bottle attached to the HP cannula for 14 to 24 days in which no other test was done. The daily standard meal consisted of 1,000g of a dog kibble (Wayne Dog Food, Allied Miles Inc., Chicago). Ingredients: protein 25% (250g), fat 8% (80g), linoleic acid 2% (20g), calcium 2% (20g), etc.) The bottle was emptied each morning. Volume and acid output were measured daily. Acid concentration was determined by titration with 0.1 N NaOH to pH 7 on an automatic titrator (Radiometer, Copenhagen). The result of each day's acid production was expressed in milliequivalents.

2.    Five Hour Acid, IR-Ga, IR-GIP, IRI and Glucose Responses To A Meat Meal Alone.

Before each test the dog was fasted for at least 18 hours. For one hour before each test the GF was kept open to ensure that the dog's stomach was entirely empty. The dog was then allowed to stand in the dog

stand with a support under the dog's abdomen to prevent the dog from
sitting down.

An i.v. infusion line was introduced into the large vein on the
anterior aspect of the fore limb for blood samples. Infusions of 154 mM
NaCl were delivered through polyethylene tubing into the leg vein. A
peristaltic pump (Harvard Apparatus Company, Dover, Mass.) maintained the
infusion at 60 ml/hr. Each dog was tested either twice or three times per
week. There was always at least 48 hours between each test. A modified
washout technique was used to collect accurately the secretion of the HP:
At the end of each 15 minute collection period, 50 ml syringe was
connected to the stainless canula and 20 ml of physiological saline was
instilled into the HP using the syringe to irrigate gently the HP twice.
The volume of each sample was measured to within 0.2 ml, and total acid
was determined as stated above. Basal secretion from HP was collected for
two 15 minute periods.

A measured 15 oz (425 g) meat meal (Dr. Ballard's Dog Food, Standard
Brands Ltd., Canada. Ingredients: protein 9% (38g), fat 5% (21g)) were
given to each dog. For five hours following the standard meat meal, HP
secretion was collected at 15 minute intervals. The GF was kept closed
during the feeding experiments.

Each dog had venous blood drawn for serum IR-Ga, IR-GIP, IRI and
glucose determinations at fasting, 15, 30, 45, 60, 90, 120, 150, 180, 210,
270 and 300 minutes following the meal. Blood samples were centrifuged
within one hour, the serum separated and kept frozen until IR-Ga, IR-GIP,

IRI and glucose determinations were performed. The standard meal stimulations were performed twice in each dog.

3.  Effect of Ingestion of Fat (Unhydrolyzed and Hydrolyzed) on Five Hour Acid, IR-Ga, IR-GIP, IRI and Glucose Responses to a Meat Meal.

125g of cream (Silverwood Shipping Cream, Silverwood Dairies, Toronto, Canada. Ingredients: protein 2.6g; fat 38.2g; saturated fatty acids 21.4g; oleic acid 13.1g; linoleic acid 1g; carbohydrate 4.2g; calcium 0.1g) was mixed with 15oz standard meat meal and ingested within three minutes.

On another occasion, the same amount of cream was incubated with three capsules of Cotazymes (Organon Co., Toronto, Canada: each capsule contains 800 units of pancreatic lipase) for three hours at 37°C (hydrolyzed fat) (see APPENDIX) and mixed with 15oz standard meat meal and ingested within three minutes.

For five hours following the meat meal mixed with unhydrolyzed or hydrolyzed cream, HP secretion was collected at 15 minute intervals. The volume of each sample was measured, and total acid was determined as described above. Venous blood was drawn for serum IR-Ga, IR-GIP, IRI and glucose determinations at fasting, 15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 270, and 300 minutes following the meal. Those tests were each performed twice in each dog.

4.    Serum Glucose and IRI Responses to i.v. Glucose Load, and Serum

Glucose, IRI and IR-GIP Responses to Intragastric Glucose Load.


Pancreatic endocrine function was examined by i.v. and intragastric

glucose tolerance tests with dextrose solution (1g/kg body weight) and

Pal-a-dex 100 (J. T. Baker Chemical Co., Phillipsburg, New Jersey; 2g/kg

body weight), respectively.  50% dextrose solution with an equal volume of

saline was infused over a two to four minute period.  Pal-a-dex was given

intragastrically by means of the GF.


Under fasting conditions for at least 18 hours, peripheral venous

blood was sampled at pre-injection, 15, 30, 45 and 60 minutes after i.v.

glucose load, and at fasting, 15, 30, 60, 90, 120, 150, and 180 minutes

after intragastric glucose load.  The tests were performed twice in each

dog.  Blood samples were centrifuged within one hour, the serum separated

and kept frozen until glucose, IRI, and IR-GIP determinations were

performed.


After completing all the control studies, PDL was performed on all

dogs:  under general intubation anesthesia, both the major and minor

pancreatic ducts were ligated, and the pancreas was separated from the

duodenum by interposition of the omentum.  Following PDL, the first series

of tests was repeated:  24 hour study was started one week after PDL and

five hour acid, IR-Ga, IR-GIP, IRI and glucose in response to meal

ingestion were estimated at four to eight weeks (six weeks in average)

after PDL, while[1] serum glucose and IRI in response to i.v. glucose, and[2]

serum glucose, IRI and IR-GIP in response to intragastric glucose were

estimated at two and ten weeks, and two weeks after PDL, respectively.

Liver function tests were performed ten days and six weeks after PDL on all of four dogs. Serum glutamic oxaloacetic transaminase was slightly increased in three of four dogs, serum alkaline phosphatase slightly to moderately increased in all dogs, and serum albumin slightly increased in three of four dogs. Changes of serum amylase and calcium were not consistent.

Body weight of the dogs was stationary to slightly increased except one dog in which marked loss of body weight was observed. Marked steatorrhea was not observed in any dog.

After completing all tests following PDL, autopsy was performed on all dogs. Marked atrophy of the pancreas and mild to moderate hemorrhagic gastroduodenitis were observed in all dogs studied.

5. Assays.

Serum IR-Ga, IR-GIP and IRI concentrations were measured in duplicate using the Schwarz/Mann Gastrin Radioimmunoassay Kit, the method of Kuzio et al,[19] and the Amersham Radioimmunoassay Kit, respectively; and serum glucose concentrations using a Beckman glucose analyzer.

The cross reactivity check of the GIP antibody, GPO1 (purchased from Dr. J. C. Brown, University of British Columbia), is as follows: motilin, 0.1%; insulin, 0.02%, C-ter GIP minus), 135%; N-ter GIP minus), 1.0%;

CCK, 1.1% VIP, 0.05%, secretin and glucagon, no cross reactivity.
Integrated acid, IR-Ga, IR-GIP, IRI and glucose responses were calculated
as previously described (20). Results are given as mean ± standard error
of the mean (SEM). GP01 was a reliable antibody, but it was discovered
subsequent to the completion of this work, that it recognized only one of
the G.I.P. moieties and our levels are therefore lower than those using an
antiserum that recognized both.

Statistical comparisons between mean responses on the different
stimulations and between pre and post PDL conditions were made using the
multiple comparison method of Scheffe.[21]. Values of less than 0.05 were
considered statistically significant.

RESULTS

1.    Twenty Four Hour Study.

Twenty four hour HP acid outputs increased significantly ($p < 0.05$) in each of the four dogs after PDL (Fig. 1). This rise occured one to two weeks postoperatively in all dogs studied.

2.    Five Hour Acid, IR-Ga, IR-GIP, IRI and Glucose Responses to a Meat Meal Alone.

The mean fasting HP acid outputs were not significantly different in the pre and post-pancreatic duct ligated dogs ($0.038 \pm 0.010$ mEq/15 minutes before PDL vs. $0.061 \pm 0.030$ mEq/15 minutes after PDL). The mean peak acid outputs from the HP before and after PDL were $0.664 \pm 0.174$ mEq/15 minutes at 150 minutes and $0.719 \pm 0.124$ mEq/15 minutes at 135 minutes, respectively. Following PDL, the HP acid was augmented, but there was no significant difference at each of the time points (Fig. 2). Integrated HP acid outputs during five hour period after the meat meal were greater than those prior to PDL ($98 \pm 27$ mEq/five hours before PDL vs. $113 \pm 34$ mEq/five hours after PDL), but with no significant difference.

The mean fasting serum IR-Ga concentrations in the four dogs after PDL were lower than those before PDL but not statistically significant ($103 \pm 12$ pg/ml before PDL vs. $86 \pm 13$ pg/ml after PDL). The mean IR-Ga concentrations were lower in the PDL dogs than in the control dogs, but

the difference was not stastically significant (Fig. 3).

No significant differences in basal IR-GIP concentrations were found between the pre and post-PDL dogs. The mean peak IR-GIP concentrations before and after PDL were 468 ± 52 pg/ml at 60 minutes and 610 ± 110 pg/ml at 60 minutes after PDL, respectively, and the difference was statistically significant ($p < 0.05$) Fig. 4). Integrated serum IR-GIP response during the five hour period following the meat meal alone was significantly greater than that prior to PDL (28 ± 10 ng/ml/five hours before PDL vs. 63 ± 15 ng/ml/five hours after PDL, $p < 0.05$).

Multiple comparison procedure revealed significant decrease in the IRI secretion after PDL ($p < 0.05$) (Fig. 5).

The mean serum glucose concentrations at each of the subsequent time points in the dogs after PDL significantly exceeded those prior to PDL (Fig. 6).

3.   Five Hour Acid, IR-Ga, IR-GIP, IRI and Glucose Responses to a Meat Meal Plus Unhydrolyzed Cream.

After feeding a meat meal plus cream the peak acid output from the HP prior to PDL occured at 150 minutes (0.0576 ± 0.227 mEq/15 minutes), and remained almost at the same level for the remainder of the two hour period. After PDL acid response essentially did not change except for a small increase after 135 minutes (Fig. 7). Integrated acid response during the five hour period following the meal after PDL was

insignificantly greater than that prior to PDL (121 ± 45 mEq/five hours before PDL vs. 137 ± 51 mEq/five hours after PDL).

The mean five hour serum gastrin concentrations after PDL were lower than before PDL (Fig. 8) but integrated five hour serum IR-Ga response to the meal after PDL was greater than that prior to PDL vs. 8.6 ± 3.2 ng/ml/five hours after PDL (5.4 ± 2.3 ng/ml/ five hours before PDL), although there was no significant difference.

Following the meal, the mean serum IR-GIP concentrations were lower in the dogs after PDL than before PDL. The peak IR-GIP response was significantly lower after PDL (844 ± 67 pg/ml before PDL vs. 655 ± 129 pg/ml after PDL, p < 0.05) (Fig. 9). Integrated serum IR-GIP response to the meal during the five hour period after PDL was significantly lower than that prior to PDL (144 ± 21 ng/ml/five hours before PDL vs. 116 ± 23 ng/ml/ five hours after PDL, p < 0.05).

Before PDL integrated serum IR-GIP response to a meal plus unhydrolyzed cream during the five hour period was significantly higher than that to a meat meal alone (144 ± 21 vs. 28 ± 10 ng/ml/five hours, p < 0.01) and after PDL integrated serum IR-GIP response to a meat meal plus unhydrolyzed cream during the five hour period was also higher than that to a meat meal alone but not significant (116 ± 23 vs. 63 ± 15 ng/ml/ five hours).

Following the meal the mean serum IRI concentrations at each subsequent time point in the dogs after PDL were lower than those prior to

PDL. The time of the peak value of serum IRI concentrations was almost identical to that of serum IR-GIP concentrations (Fig. 9 and 10).

The mean serum glucose concentrations at each subsequent time point except at 60 minutes following the meal in the dogs after PDL were lower than those in the same dogs prior to PDL, and the difference was significant at 300 minutes (86 ± 3 vs. 98 mg/dl, p 0.05) (Fig. 11).

4.    Five Hour Acid, IR-Ga, IR-GIP, IRI and Glucose Responses to a Meat Meal Plus Hydrolyzed Cream.

For the 135 minute period following the meal the mean acid response from the HP was lower than that prior to PDL, but not statistically significant. The peak acid outputs from the HP before and after PDL were 0.990 ± 0.348 mEq/15 minutes at 120 minutes and 0.991 ± 0.270 mEq/15 minutes at 195 minutes, respectively (Fig. 12). Integrated HP acid output during the five hour period after PDL was smaller than that prior to PDL (198.39 mEq/five hours before PDL vs. 176.73 mEq/five hours after PDL), but there was no significant difference.

Integrated serum IR-Ga response during the five hour period after PDL was smaller than that prior to PDL (9.9 ± 4.0 ng/ml/five hours before PDL vs. 4.6 ± 1.8 ng/ml/five hours after PDL), but there was no significant difference.

The mean serum IR-GIP concentrations during the 60 minute period following the meal after PDL were almost identical to those prior to PDL,

and they remained lower thereafter compared to those prior to PDL (Fig. 14). Integrated serum IR-GIP response to the meal during the five hour period after PDL was insignificantly smaller than that prior to PDL (152 ± 18 ng/ml/five hours before PDL vs. 119 ± 23 ng/ml/five hours after PDL).

Serum IR-GIP response to meat meal plus hydrolyzed cream after PDL was very similar to that of meat meal plus unhydrolyzed cream after PDL. Before PDL, integrated serum IR-GIP response to meat meal plus hydrolyzed cream during the five hour period was significantly higher than that to meat meal alone (152 ± 18 vs. 28 ± 10 ng/ml/five hours, $p < 0101$), and almost identical to that of meat meal plus unhydrolyzed cream (152 ± 18 vs. 144 ± 21 ng/ml/five hours). After PDL, integrated serum IR-GIP response to meat meal plus hydrolyzed cream during the five hour period was insignificantly higher than that to meat meal alone (119 ± 23 vs. 63 ± 15 ng/ml/five hours).

The mean serum IRI concentrations following the meal after PDL was almost identical to those prior to PDL (Fig. 15).

For the 180 minute period following the meal after PDL, the mean serum glucose response was greater than prior to PDL, but the difference was not significant (Fig. 16).

5.    Serum Glucose and IRI Responses to i.v. Glucose Load.

The mean serum glucose concentrations following i.v. glucose were significantly higher in the post-PDL dogs than in the same dogs prior to

PDL at 15, 30, 45, and 60 minutes (326 ± 12 vs. 205 ± 9 mg/dl at 15

minutes, two weeks after PDL, $p < 0.01$; 338 ± 30 vs. 205 ± 9 mg/dl at 15

minutes, ten weeks after PDL, $p < 0.01$; 218 ± 13 vs. 100 ± 5 mg/dl at 30

minutes, two weeks after PDL, $p < 0.001$; 230 ± 6 vs. 100 ± 5 mg/dl at 30

minutes, ten weeks after PDL, $p < 0.001$; 155 ± 11 vs. 72 ± 3 mg/dl at 45

minutes, two weeks after PDL, $p < 0.001$; 170 ± 4 vs. 72 ± 3 mg/dl at 45

minutes, ten weeks after PDL, $p < 0.001$; 115 ± 6 vs. 80 ± 4 mg/dl at 60

minutes, two weeks after PDL, $p < 0.001$; 140 ± 5 vs. 80 ± 4 mg/dl at 60

minutes, ten weeks after PDL, $p < 0.001$) (Fig. 17).


The mean serum IRI concentrations were significantly lowered after

PDL (40.4 vs. 24.3 μU/ml at 15 minutes, two weeks after PDL, $p < 0.05$;

40.4 vs. 16.1 μU/ml at 15 minutes ten weeks after PDL, $p < 0.05$; 30.8 vs.

15.8 μU/ml at 30 minutes, two weeks after PDL, $p < 0.05$; 30.8 vs. 11.3

μU/ml at 30 minutes, ten weeks after PDL, $p < 0.05$; 18.4 vs. 10.4 μU/ml at

45 minutes, two weeks after PDL, $p < 0.05$; 18.4 vs. 9.6 μU/ml at 45

minutes, ten weeks after PDL, $p < 0.5$).


In contrast, the mean serum IRI concentration at 60 minutes

following i.v. glucose was significantly increased ten weeks after PDL

(8.8 vs. 26.0 μU/ml, $p < 0.05$) (Fig. 18).

6.  Serum Glucose, IRI, and IR-GIP Responses to Intragastric Glucose
    Load.

The mean fasting serum glucose values before and after PDL were 68 ±
4 mg/dl and 79 ± 4 mg/dl, respectively, and the difference was not
statistically significant. After PDL, the mean serum glucose
concentrations were significantly lower at 15 minutes (110 ±7 vs. 159 ± 15
mg/dl, p < 0.05), at 30 minutes (122 ± 10 vs. 183 ± 11 mg/dl, p < 0.01),
and at 45 minutes (138 ± 12 vs. 175 ± 11 mg/dl, p < 0.05) following
intragastric glucose load and reached peak values at a later time (155 ±
10 mg/dl at 90 minutes after PDL and 183 ± 11 mg/dl at 30 minutes before
PDL), persisting higher levels than prior to PDL (151 ± 12 vs. 87 ± 8
mg/dl at 120 minutes, p < 0.01; 116 ± 14 vs. 83 ± 6 mg/dl at 150 minutes,
p < 0.05) (Fig. 19).

There was no significant difference between the mean peak glucose
values before and after PDL, and thus only showing the delayed pattern
after PDL. There was also no significant difference between the mean
integrated glucose response before and after PDL (10211 ± 1213 mg/dl/180
minutes before PDL vs. 9180 ± 1184 mg/dl/180 minutes after PDL). The mean
serum IRI response was higher at each time point after 60 minutes
following glucose load after PDL, and the difference was significant at
120 minutes (11.8 µU/ml before PDL vs. 26.8 µU/ml after PDL, p < 0.05).
The mean integrated IRI responses were 843 ± 192 µUml/180 minutes before
PDL and 764 ± 164 µU/ml/180 minutes, and there was no statistical
difference.

The mean serum IR-GIP response after PDL remained rather higher for the latter 120 minute period than before PDL. The pattern of serum IR-GIP response was very similar to that of serum IRI response (Fig. 21). The mean integrated serum IR-GIP response after PDL was greater than that before PDL 37.3 ng/ml/180 minutes before PDL vs. 51.5 ng/ml/180 minutes after PDL), but was not significant.

DISCUSSION

(A)   GASTRIC SECRETION

Gastric hypersecretion in the dog following pancreatic duct ligation (PDL) is a well recognized phenomenon.  However, the mechanism behind it has not yet been defined.  The possibility that the pancreas with obstructed ducts produce a gastric secretagogue, namely a gastrin-like substance, has been disproved by bioassay and immunoassay of the atrophic pancreas for gastrin.  Menguy ascribed gastric hypersecretion following PDL to secondary liver damage[22].  The maldigestion of fat and malabsorption of essential fatty acids was thought to be a cause of hepatic damage and gastric hypersecretion.

It has been suggested that an augmented gastrin response to feeding is a primary factor in the production of gastric hypersecretion occuring when pancreatic enzymes are excluded from the digestive stream,[1] whereas Greenlee[4] considered gastrin is not a main factor as after antrectomy, PDL still produces an increase in gastric acid.  Although the increase in daily acid secretion from the HP observed in response to the ingestion of an ordinary meal after PDL confirms the previous observation of others,[2,23] there was only a modest increase of HP acid and decrease of gastrin response to a meat meal after PDL as compared to that before PDL. These findings differ from others who reported an augmented gastrin response as well as an augmented HP acid response to feeding in dogs after PDL.[1,23]  These discrepancies are hard to explain, but may be due, at least in part, to the different conditions of the experiments; in the present experiment the dogs were fed with cream (unhydrolyzed and

hydrolyzed) mixed with ordinary meals which might have resulted in the different secretary responses. Wormsley and Grossman[24] observed that closing the GF produced marked inhibition of the response of the HP to stimulation, suggesting endogenous inhibition related to passage of acid from the main stomach into the duodenum. The GF was kept closed during the present study, and although acidity of the main stomach after meal ingestion was not measured, postcibal gastrin release from the antrum and duodenum was probably suppressed by antral and duodenal hyperacidity caused by an as yet unknown mechanism following PDL. Antral acidification is known to inhibit gastrin release,[25] but it is unknown whether acid directly suppresses the G cells or whether it releases an inhibitor of gastrin release from the antral mucosa. It has been shown that when innervated antral pouches were perfused with acid or alkaline solutions in dogs with a HP using chemical or vagal stimulation of the antrum, gastrin-like immunoreactivity appeared in all perfusates but was found to be seven times higher in the acid perfusates, indicating the acidification of the antrum may not block release of gastrin, but it may change the direction of release and divert gastrin from the circulation to the antral lumen[26]. Some workers have postulated that acid in the pyloric gland area caused release of an antral inhibitory hormone "antral chalone"[27,28] that suppresses the activity of the oxyntic cells, but its physiological significance, if any, is still to be studied. A possible explanation of some of the findings could be that new dogs were debilitated by pancreatitis or other operative trauma. I feel however that this does not match with our observations. Only one of the four dogs lost weight, the others were all healthy and ate well. Autopsy, too, disclosed no significant abnormalities apart from some adhesions and very mild

inflammation. (Photo 1)

Gastric and duodenal acidification results in a marked rise in the plasma level of somatostatin.[29] Somatostatin may be involved in the antral and duodenal inhibitory mechanisms but further studies are needed to determine the physiological role of this peptide in antral and duodenal feedback inhibition of gastric secretion.

The name bulbogastrone has been given to a hypothetical humoral factor[30] secreted from the duodenal bulb where pH dependent gastric acid inhibition operates. The mechanism seems to suppress acid secretion by interfering with the stimulatory action of gastrin at the oxyntic glands and whether bulbogastrone inhibits gastrin release is unknown.

The principal humoral mechanism of gastric acid inhibition by duodenal acidification is the release of secretin from the endocrine S cells in the duodenal mucosa, and it has been demonstrated that the inhibition of gastric acid secretion by endogenous or exogenous secretion is brought about by blocking the action of gastrin at the parietal cell level through a non-competitive mechanism.[31] Tasse et al[32] showed that the serum gastrin levels in dogs having undergone the Exalto-Mann-Williamson procedure remains unchanged, whereas the plasma secretin concentrations in these animals are increased, indicating alterations in circulatory secretin or gastrin are not responsible for the gastric acid hypersecretion following the procedure, and postoperative hypersecretinemia would be caused by stimulation of secretin release from the gut mucosa secondary to enhanced secretion of gastric acid. Secretin

was shown to suppress the release of gastrin in response to food in dogs.[33] There have been no studies of secretin secretion after PDL, but it has been shown that exclusion of pancreatic juice in dogs with pancreatic fistula resulted in augmented plasma secretin response to meal ingestion.[34] It seems reasonable to assume that marked acidification of the post bulbar duodenum well below 4.5 (the threshold for secretin release in the dog) releases enough secretin to inhibit gastrin release and subsequently suppress the HP acid secretion after PDL.

It has been shown that cholecystokinin (CCK) is predominantly the inhibitory hormone released by strong acidification of the duodenum. Kakajima and Magee showed that duodenal acidification over a pH range of seven to three released mainly secretin and, at a lower pH, mainly CCK.[35]

Suppression of gastrin release is brought about by all members of secretin family of hormones (glucagon, vasoactive intestinal polypeptide (VIP), and GIP) and by one chemically unrelated peptide, calcitonin. All these hormones also exert a direct inhibitory action on the perietal cells. The question of whether these humoral factors inhibit release of gastrin under physiological conditions is not settled. Possible role of GIP in regulating gastric acid and gastrin will be discussed later in this part of the communication.

Thus the suppressed gastrin response caused by the possible mechanisms as mentioned above was probably, at least partly, responsible for the only modest increase in the five hour HP secretion. Also these findings indicate that the intestinal phase of gastric secretion may have

been more markedly augmented after PDL than gastric phase of acid secretion by the mechanism that the persistence of undigested and unabsorbed food products in the small intestine results in inappropriately prolonged stimulation of gastric secretion. Chey at al[2] showed the most striking increase of HP acid outputs during the twelve to 24 hour period of daily meal study in PDL dogs, suggesting that both gastric and intestinal phase of gastric secretion participated in the response.

The mechanism of intestinal stimulation of gastric secretion has not yet been defined. Until recently, "intestinal gastrin" was the name generally used when referring to the mediator of the intestinal phase. This term is unsatisfactory since several different substances may be involved in the intestinal phase of gastric secretion, namely "entero-oxyntin", an antral type of gastrin, CCK, and histamine. Experimental studies suggest that the main intestinal phase stimulant is an as yet unidentified hormone from the intestinal mucosa, for which the name "entero-oxyntin" has been proposed.[24] "Entero-oxyntin" is the principal hormone responsible for the intestinal phase of gastric secretion, having unique pattern of gastric stimulation that cannot be accounted for by gastrin, CCK, or histamine. To date, no studies have been performed to determine the possible role of CCK and histamine in the intestinal phase of gastric secretion.

Konturek et al[36] noted a marked rise in serum gastrin level and a potent stimulation of gastric secretion during intestinal perfusion of liver extract meal, and suggested the intestinal meal stimulates gastric secretion by a mechanism involving the release of antral hormone.

Thompson et al[37] speculated that liver extract meal in the intestine may release a bombesin-like substance (entero-bombesin) that, in turn, releases antral gastrin. Orloff et al[38] have recently isolated the intestinal phase hormone (IPH) from hog intestinal mucosa. IPH is not gastrin and augments the maximum gastric secretory response to gastrin.

It is well documented that fat added to the meal in the duodenum suppressed the acid secretion of transplanted pouches[6] indicating that the inhibition was humorally mediated and Kosaka and Lim[7] proposed the name "enterogastrone" for the humoral inhibitor agent. Quigley and Meschan[39] showed that the products of lipolysis were more potent inhibitors of gastric motility than corresponding neutral fat, and the observation of Sircus[40] indicates that fats exerts their effect only if pancreatic juice is present. It is well known that pancreatic lipase plays a dominant role in fat absorption, and triglyceride is hydrolyzed by lipase to fatty acids and glucerol.

GIP obtained from an extract of duodenal mucosa has been isolated, purified, and chemically characterized.[15] This substance inhibits gastric acid and pepsin secretion stimulated by pentagastrin, histamine, and by insulin-hypoglycemia in dogs,[8] and also inhibits spontaneous motor activity of denervated fundic and antral pouches, qualifying as an enterogastrone. It has been speculated that a disturbed GIP release may be responsible for the abnormal acid release in duodenal ulcer disease. Contrary to this assumption, an exaggerated GIP release following oral glucose or the test meal was observed in patients with duodenal ulcer.[11,12] It was suggested that rapid gastric emptying or increased

intestinal motility is responsible for the increased GIP secretion.[11]
Cataland et al[12] claimed that the possibility that patients with duodenal
ulcer may release a form of GIP with weak gastric acid inhibitory
properties. The prime role of GIP is to potentiate glucose-induced
insulin release,[15] and there is still some controversy as to whether GIP
has the enterogastrone-like effect. In innervated stomach preparations of
the dog[9] and in normal man[10] inhibition of pentagastrin-stimulated acid
secretion by GIP was found to be weak. The possible involvement of a
cholinergic mechanism antagonistic to the action of GIP on the stomach has
been suggested by the observation that the acid inhibitory effect of this
hormone in the denervated gastric pouch of the dog can be blocked by the
i.v. infusion of urecholine.[9] An explanation for these observations that
GIP does not exert its inhibitory effect directly on the parietal cell but
rather indirectly via the release of an inhibitor, from the corpus of the
stomach which is also under cholinergic control. McIntosh et al[41] proposed
that the acid inhibitory activity of GIP is probably mediated via release
of gastric somatostatin-like immunoreactivity.

Ebert et al[14] demonstrated that intraduodenal infusion of HCl
dose-dependently released GIP in humans and rats, while Brown et al[15]
failed to show IR-GIP release in dogs by HCl. LeRoith et al[16] showed that
HCl by itself is capable of stimulating GIP, suggesting physiological
significance of acid induced GIP secretion. It has been shown by Spitz et
al[42] that when HCl is added to an oral glucose load, the blood levels of
glucose, GIP and insulin were higher than after glucose alone. Augmented
GIP release after intra-duodenal administration of glucose was observed
when exogenous gastrin, pentagastrin, and CCK were given.[43] Flaten[44] on

the other hand, studied the effect of duodenal acidification on the glucose-stimulated GIP or insulin release in man and showed no augmentation of GIP or insulin by duodenal acidification. The conflicting results from previous studies seem to indicate the importance of gastric emptying as well as species difference in GIP secretion after duodenal acidification. A reason for the augmented GIP secretion, which is the most important finding of the present study, in the dogs after PDL administered meat meal alone could be increased acid secretion coming into the duodenum and the upper intestine.

Another explanation for the increase of IR-GIP response to a meat meal alone after PDL is a change of gastrointestinal motility. It has been shown by Fauley and Ivy that the emptying time of the stomach is decreased by PDL in dogs and the authors suggested that hunger, or polyphagia, is the factor principally concerned in the causation of the decrease,[45] and Yesco[46] described a similar result. Long et al[47] described abnormally rapid gastric emptying of liquid fatty meals in pancreatic insufficiency and ascribed it to maldigestion, while Regan et al[48] showed no primary gastric motor defect in patients with exocrine pancreatic insufficiency. The discrepant finding of these studies seems to be due to differences of the technique used for the measurement of gastric emptying. CCK and secretin have been shown to inhibit gastric motility in dogs.[49] CCK was found to be increased in pancreatic insufficiency.[50] In the present study, although CCK and secretin concentrations were not measured, both hormones might have been increased in the dogs after PDL as above discussed.

It seems to be an intriguing hypothesis, therefore, that gastric motility was decreased after PDL by augmented secretion of some gut peptide such as CCK and secretin. In the present study, gastric emptying was not measured, but as shown in Fig. 19, gastric empyting was probably delayed after PDL. Oral glucose tolerance test has been suggested for the assessment of gastric emptying.[51] If so, this is noteworthy, as the results of the present study do indicate that marked lowering of pH of duodenal contents due to augmented acid secretion together with lack of alkaline (pancreatic) juice after PDL is responsible for the augmented GIP release from the intestinal mucosa.

Patients with chronic pancreatitis were shown to have a significantly higher GIP response to a test meal.[52] The authors suggested that the elevated IR-GIP levels seen in patients with chronic pancreatitis could be due to lack of inhibition of IR-GIP release by insulin, and concluded that perhaps IR-GIP release to a test meal was dependent upon the rate of absorption of nutrient (fat) and the capacity of the Θ-cell to secrete insulin. The most important finding of the present study that the greatly increased GIP after PDL in response to meat meal alone but somewhat decreased for fat (unhydrolyzed and hydrolyzed) cannot be explained by a lack of negative feedback inhibition of IR-GIP by insulin, because serum IRI response after PDL was more lowered in response to the cream-added meal than to the meat meal alone.

GIP is released after ingestion of glucose, fat, and amino acid, and fat is a most powerful stimulus for GIP release.[15] Fat has to be hydrolyzed before GIP release is initiated. It has been shown that long

chain fatty acids, rather than glycerol, stimulates GIP release.[15] Fatty acids must be absorbed and metabolized by the GIP producing céll. The exact mechanism whereby the absorption caused release is not known. Ross et al[53] observed that children with cystic fibrosis had three fold increase in IR-GIP secretion if given pancreatic enzymes while ingesting the triglyceride, while they had no IR-GIP response to triglyceride only, and suggested that hydrolysis of triglyceride is required before GIP release can normally occur after fat ingestion.

IR-GIP response to a meat meal was markedly augmented by mixing unhydrolyzed cream: the peak IR-GIP concentrations and the integrated IR-GIP response to an unhydrolyzed cream-added meal was significantly greater than those to a meat meal alone indicating greater amount of GIP was released by adding fat. After PDL, IR-GIP response to a meat meal plus unhydrolyzed cream was significantly reduced, and this indicates that GIP was not properly released by fat due to failed hydrolysis to fatty acid by lack of pancreatic lipase. It can of course not be excluded that GIP secretion was suppressed by other yet unidentified gut peptides or neural mechanisms which were released or augmented by clocking pancreatic external secretion.

Again, presumably augmented acid secretion may have occurred in the main stomach following the fat-added meal ingestion after PDL, and GIP secretion was augmented by passage of acid into the intestinal lumen. This increase in GIP released by augmented passage of acid into the intestinal lumen was probably masked by the fat-induced GIP.

Another important finding of the present study is that there was no difference in the GIP response between the unhydrolyzed and hydrolyzed cream after PDL. A possible explanation for these unexpected findings is that GIP response is not determined by a single factor, but is a net result of stimulatory and inhibitory mechanisms. GIP response might be influenced by many factors, which include many kinds of regulatory peptides, identified or unidentified, intestinal motility, vagal control, etc. Some possible change of intestinal mucosal absorbability for fat should also be considered: even hydrolyzed fat might have been unable to be absorbed due to an as yet unknown mechanism after PDL, resulting in much reduced GIP response to the hydrolyzed fat mixed with the meat meal.

The HP acid response to meat meal plus unhydrolyzed cream was prolonged, although the time and the peak concentrations were similar to the case stimulated by meat meal alone. This is probably due to increased osmolarity of the ingested meal by adding fat. Cook showed inhibition of gastric emptying was related to the molar (and osmolar) concentration of amino acid: the greater the concentration, the greater the delay.[54]

The explanation for the greater HP acid secretion stimulated by ingestion of meat meal plus hydrolyzed cream than by ingestion of meat meal plus unhydrolyzed cream is not clear. Serum IR-Ga responses to both stimulations were similar except at a later period, indicating gastrin is not solely responsible for the greater HP secretion.

The attenuated HP secretion (especially in the early phase) stimulated by meat meal plus hydrolyzed cream after PDL is also difficult

to explain. Although serum IR-Ga response was most markedly decreased after PDL compared to other two stimulants, again gastrin is not solely responsible for the decrease in the HP secretion. The possibility that some gastric inhibitory hormone(s) was released by the digested fat even in the absence of pancreatic exocrine function can not be excluded. Fat induced GIP was shown to suppress meal stimulated gastrin,[43] but the possibility that GIP played any enterogastrone effect on the HP acid secretion in the present study is debatable, as there is no apparent correlation among the IR-GIP, IR-Ga and HP secretion. A "gastrin-GIP" axis is not apparent in the present study.

A possible deficiency in the protocol is the measurement of GIP using the GPO1 antiserum. This has been shown to measure a 5000 MW moiety on electrophoresis by Dr. John Brown. The measurement of this therefore results in lower amounts than in other studies using different antisera recognizing both (or more) moieties. Do these polypeptides of different molecular weights have different actions or are they released in varying amounts in response to different stimuli? Others will have to look into these questions. In defence, I contend that this is a purer antiserum than the others and reflects the results for the lower molecular weight GIP.

Thus the present study clearly indicates that defective secretion of GIP due to failed fat digestion is not responsible for the gastric hypersecretion after PDL, and another mechanism must be considered. A number of studies suggest that PDL causes hyperacidity by interfering with the inhibitory effect normally exerted by fat and its by-products. Many

studies have been performed to identify the hormones released by fat in the gut. It has been shown that fat releases CCK from the intestinal mucosa but there is little doubt that this hormone cannot be solely responsible for the inhibition, since fat induces suppression of histamine-stimulated acid secretion that cannot be reproduced by CCK or secretin regardless of the dose used.[55] VIP is another candidate for enterogastrone, and inhibits gastric acid secretion in dogs.[56] However, recent study of Holm-Benzen et al[57] showed that exogenously administered VIP is metabolized rapidly and has no effect on submaximally pentagastrin-stimulated acid secretion, indicating that VIP probably does not exert any hormonal effect on acid secretion in man. Although GIP appears to satisfy most completely the criteria for being the enterogastrone described by Kosaka and Lim, further studies are needed before a hormonal status can be ascribed to GIP and before its physiological role as the enterogastrone released by fat is proved.

(B)   GLUCOSE METABOLISM

PDL was the model first utilized by Banting and Best[58] to extract

insulin from the persistent islet, but the preservation of the islet

tissue was for at least a short period of time.  Dragstedt[59] reported that

extensive degeneration of the pancreas after occlusion of the pancreatic

duct could often lead to diabetes in dogs.  Whether the endocrine function

will finally deteriorate after PDL or not has so far been controversial.

Heptner et al[18] observed impaired glucose tolerance following the

intragastric and i.v. glucose load four to six months after PDL in dogs.

They stressed an insufficient reserve of insulin as a cause of development

of diabetes.  Little is known about functional alterations following PDL

especially concerning the early onset of diabetes.  In the present

experiment, intragastric glucose tolerance test performed two weeks after

PDL showed delayed serum glucose and IRI response, indicating gastric

motility was decreased after PDL.  The serum IRI response to i.v. glucose

was clearly diminished in the PDL dogs (two and ten weeks) indicating

failure of the initial phase of insulin release.  This finding is in

accordance with the observation of Kalk et al[60] that in patients with

severe pancreatic insufficiency IRI response to oral glucose was not

significantly lower than in the controls while that to i.v. glucose was

significantly less than in the controls.  They suggested that the

glucose-stimulated "entero-insular axis" is probably intact in these

patients, but in the diabetic patients there is clearly loss of pancreatic

beta cell sensitivity to glucose which may be due to damage to

"glucoreceptors" on the beta cell membrane or alternatively relfect a

disorder beyond the membrane level.  They also suggested that this

probably represents a disorder of the postulated glucose-stimulated acute

release insulin pool as the one to ten minute response was impaired. Further, Pupo et al[61] showed that the alloxan-diabetic dogs had significantly decreased early-phase insulin response to glucose pulses and slower plasma glucose disappearance rates, while these mildly diabetic dogs achieved comparable insulin levels and higher glucose levels during a prolonged glucose infusion than pre-alloxan control values, indicating the pattern of blunted early phase insulin secretion and continued late phase insulin secretion is not necessarily dependent on genetic determination and may be induced in mild alloxan diabetes, a model in which there is an acquired beta-cell insulin deficiency.

The finding that serum IR-GIP response to intragastric glucose load was very similar to that of serum glucose and IRI when performed at two weeks following PDL indicates that the GIP secreting mechanism as one of the "entero-insular axis" remains intact in this period after PDL.

Thus it has been shown that the PDL dogs had early onset (two to ten weeks) of diabetes, i.e., blunted early phase insulin secretion, indicating an acquired beta-cell insulin deficiency.

Diabetes is a frequent complication of chronic pancreatitis, being present in one-third or more of the patients with more advanced stage of pancreatic fibrosis and atrophy. Although Joffe et al[62] have postulated that the diabetic syndrome of chronic pancreatitis represents an example of acquired insulinopenia, recent observations suggest a selective or qualitative impairment of the response of the beta cells to glucose administration but maintenance of the insulin response to various

enterohormones.[60] The ability of the remaining beta cells to secrete insulin in response to intragastric glucose was retained in all dogs studied despite destruction of the exocrine pancreas, as evidenced by the completely atrophied pancreas after PDL, in disagreement with the hypothesis that beta cell function is dependent on the integrity of the exocrine tissue.[63] Also the finding that serum IR-GIP response to intragastric glucose was retained in spite of blunted early-phase insulin response to i.v. glucose supports the idea of Kalk et al[60] mentioned above.

Serum IRI response to meat meals with and without unhydrolyzed or hydrolyzed cream examined at six weeks after PDL were apparently impaired compared to those examined before PDL. An interesting finding is that meal stimulated IRI responses seem to be (at least partly) dependent on serum GIP secretion stimulated by the meal, qualifying GIP as an insulinotropic enterohormone, although it is known that GIP is insulinotropic only in the presence of hyperglycemia[64] and the peak glucose concentrations following the meat meal in the present study were within 100 mg/dl (euglycemia). The explanation for the GIP dependent insulin response to the meals in spite of euglycemic background is not clear from the present study.

The serum glucose response to meat meal alone was significantly increased after PDL, while decreased and unchanged serum glucose concentrations were seen in response to meat meal plus unhydrolyzed cream and meat meal plus hydrolyzed crexs, respectively. The possibility of the influence of GIP induced glucagon cannot be excluded although

controversial.[15,65]

CLINICAL OBSERVATIONS AND PROJECTIONS FOR THE FUTURE

Pancreatic ductal ligation is currently applied in clinical transplantation of the pancreas[66] and surgical procedure as an alternative to pancreatojejunostomy after pancreatoduodenectomy.[67] Powis et al[67] claimed the modified procedure is safer and less prone to exocrine and endocrine disturbances, pancreatic fistulas and stomal ulcerations than the conventional pancreatoduodenectomy, while Papachristou et al[68] showed distal pancreatectomy with duct ligation is a relatively safe procedure but after pancreatoduodenectomy the morbidity is reduced by a pancreatojejunostomy.

The major objections to the routine use of the pancreatic duct ligation procedure are that it abolishes exocrine activity and that it may impair pancreatic endocrine function.[59] These functional abnormalities arise in another pathological conditions of the pancreas besides in patients with pancreatic duct ligation. They include patients with distal pancreatectomy, pancreatoduodenectomy and total pancreatectomy for trauma, chronic pancreatitis, endocrine adenomas, and cancer. Patients whose pancreatojejunostomy have become stenosed or in whom the main pancreatic duct is obstructed by cancerous lesion and are born with atrophy of the pancreas are also included.

The pathological outcomes in common with these conditions are lost or decreased exocrine and endocrine function of the pancreas. These patients may have malabsorptive phenomena and diabetes.

Malabsorption and steatorrhea do not develop until 90 per cent of

pancreatic exocrine function is lost. With less than two per cent of
normal function steatorrhea is severe and energy malabsorption will
develop. Marked steatorrhea was not observed in the dogs studied in the
present experiment, and this is probably due to frequent administration of
pancreatic enzyme mixed with the meat meal for assessment of the secretory
evaluation after PDL. Thus replacement of pancreatic enzyme that is
distributed with meals is usually effective for malabsorption phenomena of
the pancreatic diseases.

Dragstedt[59] has reported that diabetes occurs only after resection
of 80 per cent or more of the entire pancreas. Further, Dragstedt et al[69]
have reported that the amounts of insulin required to control glycosuria
after partial pancreatectomy is much greater than that needed after total
resection of the pancreas. In diabetes mellitus, insulin secretion is
decreased and the anti-insulin system such as glucagon secretion is
stimulated. The anti-insulin system after total pancreatectomy has been
shown to be depressed and it has been suggested that diabetes after total
resection of the pancreas would not require as much exogenous insulin.[70]

It has also been reported that glucagon response to arginine
infusion decreased after pancreatoduodenectomy in patients with
periampurary cancer,[71] and Nishiwaki et al have shown that plasma
glucagon response to arginine infusion was low in dogs six months after
PDL.[72]

As stated in the DISCUSSION of the present paper, glucagon response may have been increased after PDL due to augmented GIP secretion which probably stimulates glucagon secretion.

In any case, from these observations it can be recommended that pancreatic diabetes should be treated separately depending upon etiology or background of the disease.

There has been controversy about whether or not increased gastric secretion or peptic ulcer occur in chronic pancreatitis. It seems probable that much of the controversy concerning the capacity of the patients with pancreatic disease to secrete acid reflects differences in the nature and degree of the pancreatitis. In surgical series which include mostly patients with chronic pancreatitis sufficiently severe to require operation, an increased incidence of ulcer has been reported. On the other hand, Hashida et al[73] have recently reported the Kyoto University experience with complete ductal obstruction due to pancreas head cancer as evidenced by ERCP or resected specimen: 33 cases were measured gastric secretion using Pentagastrin, and it was revealed that 21 patients were anacid, 11 patients had normal acid levels, and only one patient showed marked hypersecretion. They also showed that peripheral circulation of the gastric antrum was disturbed in dogs after PDL, suggesting impairment of mucosal defence is at least partly responsible for the formation of ulcer in the patients with pancreatic inflammation.

As shown in the present study, complete ductal obstruction induces gastric hypersecretion and eventually causes ulcer. There seems to be no

relationship between gastric hypersecretion and malabsorption phenomena as evidenced by no marked steatorrhea in any dog studied. However, Saunders et al[74] have reported that the presence of overt maldigestion is related to gastric hypersecretion in their patients with chronic pancreatitis. They speculated when there is much gastric juice in the duodenum and there is any residual secretion of pancreatic enzymes by patients with chronic pancreatitis, gastric juice causes rapid and irreversible denaturation of pancreatic enzymes, and the maldigestion of patients with chronic pancreatitis may be worsened. It seems wise to administer oral enzymes to all patients with extensive pancreatic disease or resection, before steatorrhea and gastric hypersecretion become manifest, as it is difficult to diagnose enzyme deficiency in the early postoperative period.

Clinical recognition of early pancreatic insufficiency is thus difficult, but may be possible by performing i.v. glucose tolerance test. As shown in the present study, glucose intolerance and decreased early phase insulin response could be a sign of early onset of pancreatic insufficiency.

Clinical implication of the result in the present study that serum IR-GIP response to the meat meal alone is significantly augmented after PDL is complex but of great importance. There have been only a few isolated case reports of marginal ulceration as a complication of pancreatoduodenectomy, while Grant et al[75] have recently reported that the overall incidence of stomal ulcer in patients submitted to a Whipple procedure or total pancreatoduodenectomy was six per cent.

Although these surgical procedures are generally known as ulcerogenic, why do so few patients get ulcers? Any study of GIP secretion after these surgical procedures has not so far been reported. The possibility that augmented GIP secretion plays some protective role against ulcer formation in these patients in co-operation with other as yet unidentified neural and hormonal factors cannot be excluded. The present study has not sufficiently verified the role of GIP in inhibiting gastric hypersecretion after PDL. Future work will elucidate the true role of GIP in the pathogenesis of gastric hypersecretion and ulcer formation in dogs after PDL and lead to practical application.

Fig.1.    24-hour acid outputs from the Heidenhain pouch
before and after pancreatic duct ligation. Each bar represents
the mean and standard error of values for 4 dogs. Number of
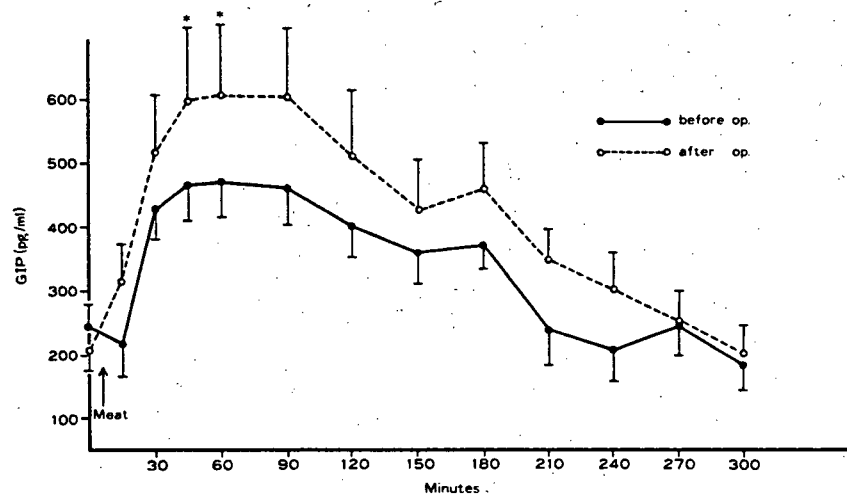experiments before and after pancreatic duct ligation for
each dog is: 18 and 29 for #1 dog; 15 and 19 for #2 dog; 21
and 25 for #3 dog; 26 and 12 for #4 dog, respectively.
*=p<0.05(significant change compared with the control period).

Fig. 2. Acid response from the Heidenhain pouch to meat meal alone before and after pancreatic duct ligation. The gastric fistula was closed during the experiment. Each point represents the mean and standard error of values for 4 dogs(8 experiments).

*Fig.3.* Serum gastrin response to meat meal alone before
and after pancreatic duct ligation. Each point represents
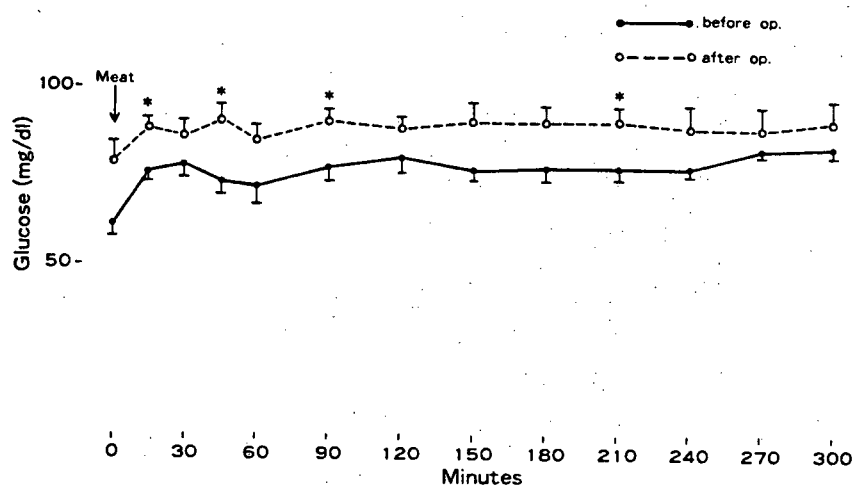the mean and standard error of values for 4 dogs(8 experiments).

*Fig. 4. Serum GIP response to meat meal alone before and after pancreatic duct ligation. Each point represents the mean and standard error of values for 4 dogs(8 experiments). \*=p<0.05(significant change compared with the control period).*
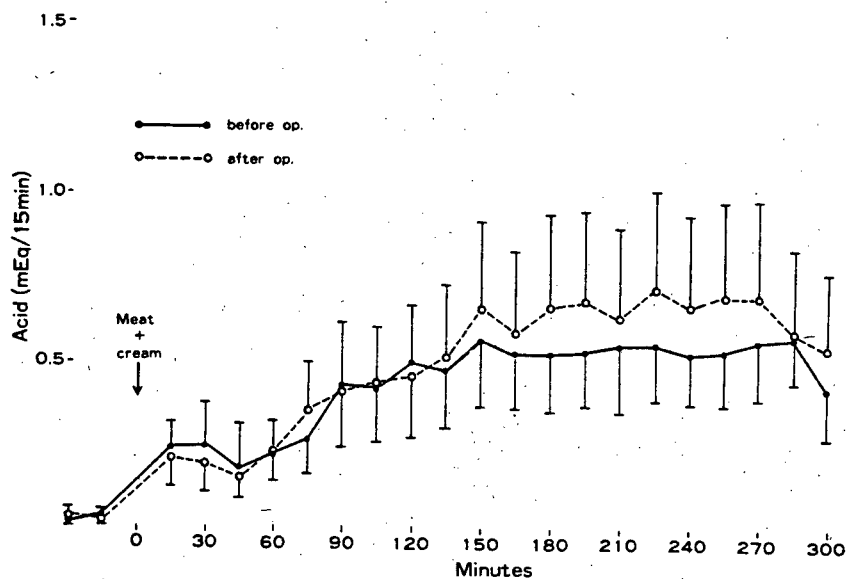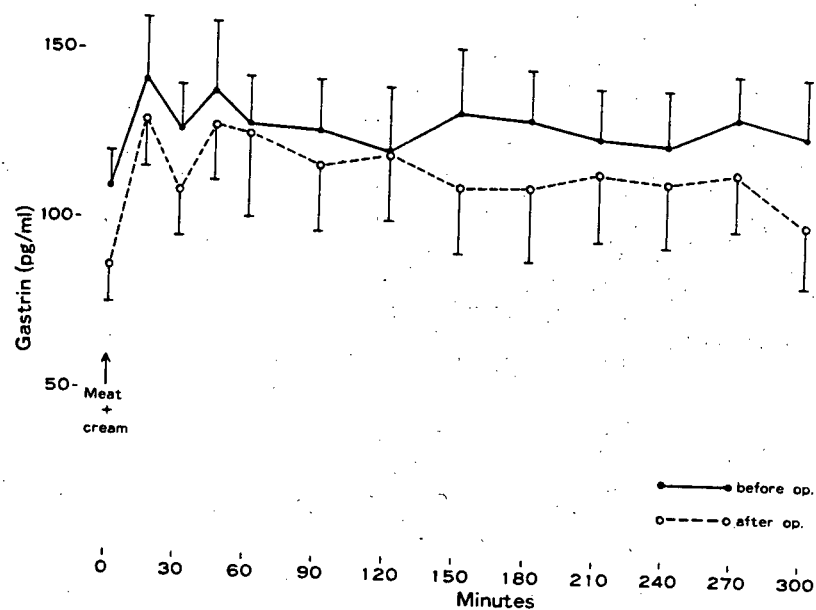
*Fig. 5     Serum IRI response to meat meal alone before and after pancreatic duct ligation. Each point represents the mean and standard error of values for 4 dogs(8 experimetns).*
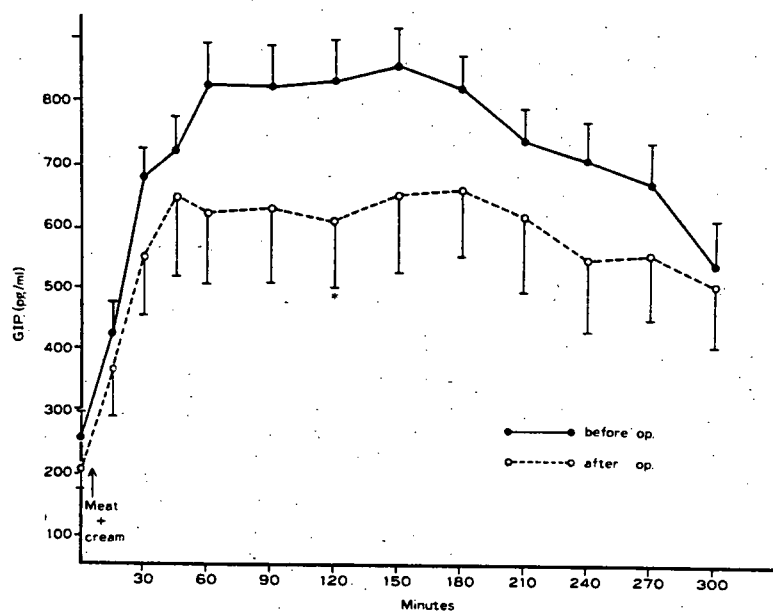
*Fig. 6    Serum glucose response to meat meal alone before and after pancreatic duct ligation. Each point represents the mean and standard error of values for 4 dogs(8 experimetns). *=p<0.05.(significant change compared with the control period).*

Fig. 7    Acid response from the Heidenhain pouch to meat meal plus unhydrolyzed cream before and after pancreatic duct ligation. The gastric fistula was closed during the experiments. Each point represents the mean and standard error of values for 4 dogs (8 experiments).

*Fig.* 8    *Serum gastrin response to meat meal plus unhydrolyzed cream before and after pancreatic duct ligation. Each point represents the mean and error of values for 4 dogs(8 experiments).*

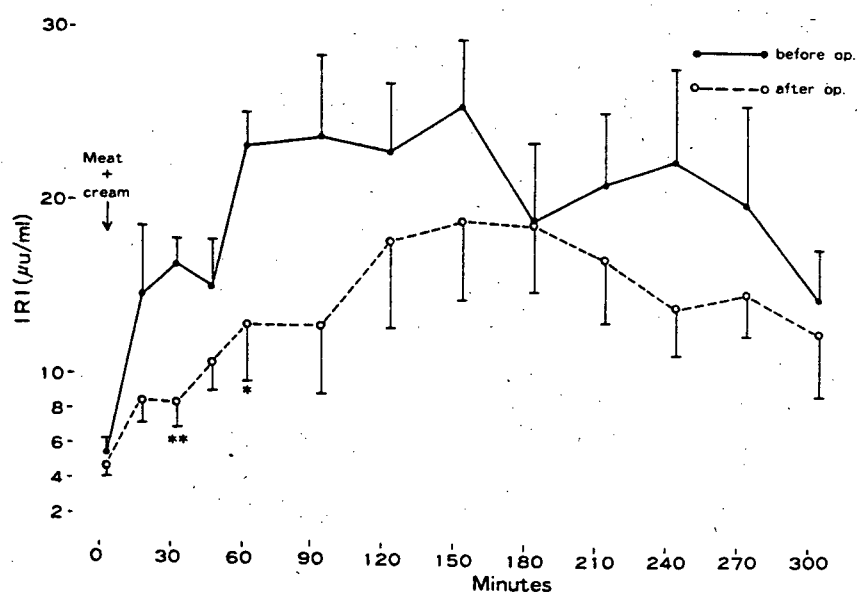Fig. 9    Serum GIP response to meat meal plus unhydrolyzed
cream before and after pancreatic duct ligation. Each point
represents the mean and standard error of values for 4 dogs
(8experiments). *=p<0.05(significant change compared with the
control period).

Fig. 10    *Serum IRI response to meat meal plus unhydrolyzed cream before and after pancreatic duct ligation. Each point represents the mean and standard error of values for 4 dogs (8 experiments).*
*\*=p<0.05,  \*\*=p<0.01 (significant change compared with the control period).*
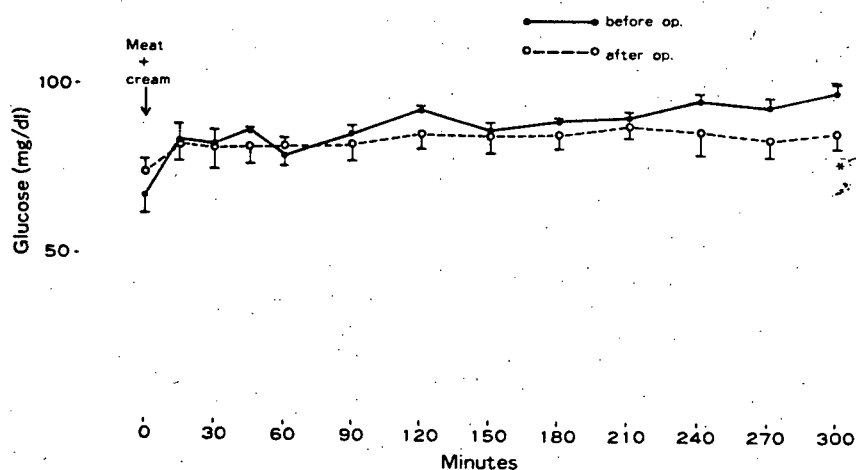
Fig.11. *Serum glucose response to meat meal plus unhydrolyzed cream before and after pancreatic duct ligation. Each point represents the mean and standard error of values for 4 dogs (8 experiments). \*=p<0.05.(significant change compared with the control period).*
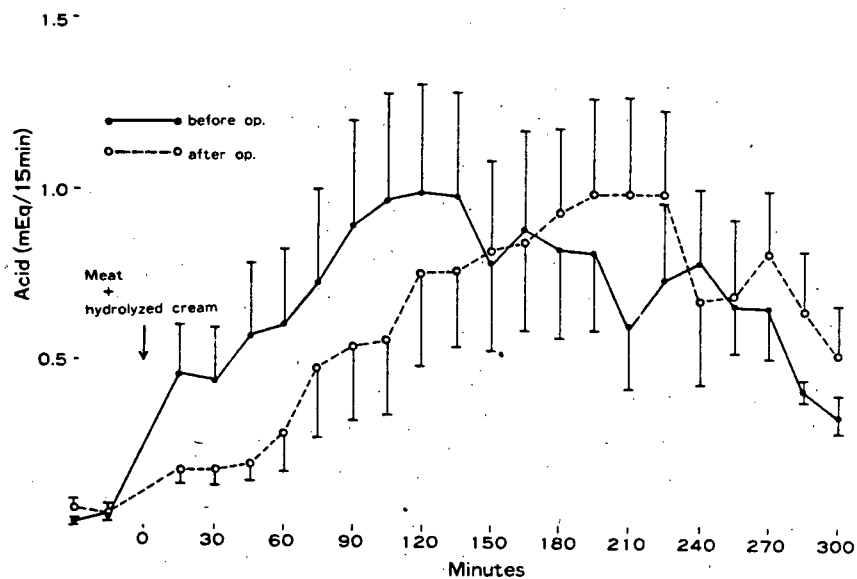
*Fig* 12 *Acid response from the Heidenhain pouch to meat meal plus hydrolyzed cream before and after pancreatic duct ligation. The gastric fistula was closed during the experiments. Each point represents the mean and standard error of values for 4 dogs(8 experimetns).*
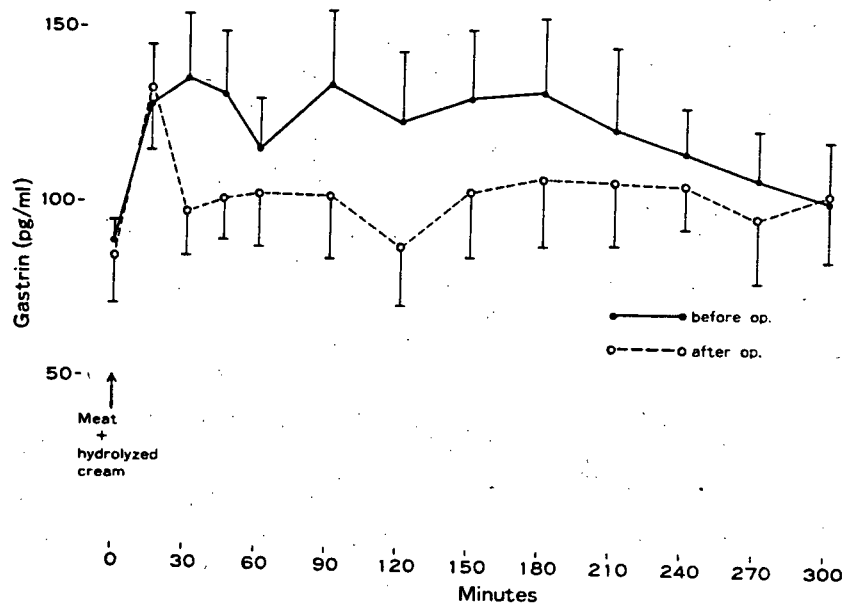
Fig. 13    Serum gastrin response to meat meal plus hydrolyzed
cream before and after pancreatic duct ligation. Each point
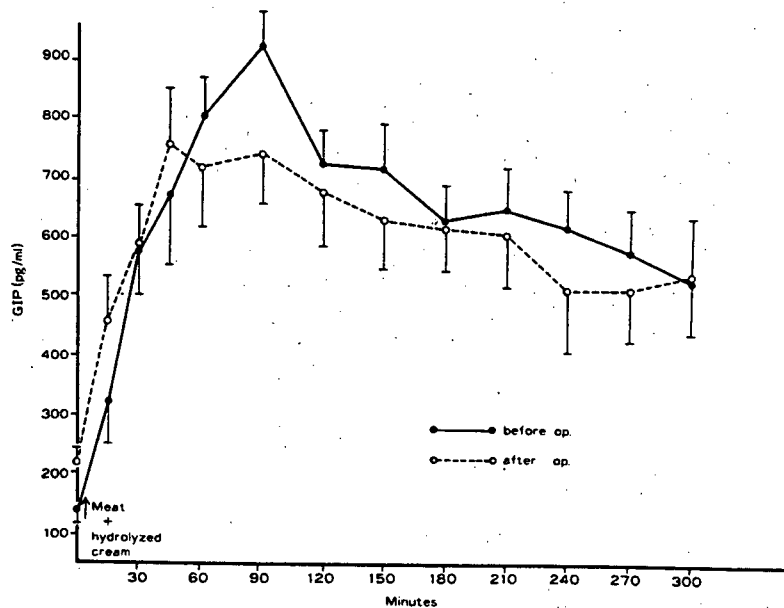represents the mean and standard error of values for 4 dogs
(8 experimetns).

*Fig.* 14   *Serum GIP response to meat meal plus hydrolyzed*
*cream bofore and after pancreatic duct ligation. Each point*
*represents the mean and standard error of values for 4 dogs*
*(8 experiments).*

*Fig.* 15   *Serum IRI response to meat meal plus hydrolyzed cream before and after pancreatic duct ligation. Each point represents the mean and standard error of values for 4 dogs (8 experiments).*
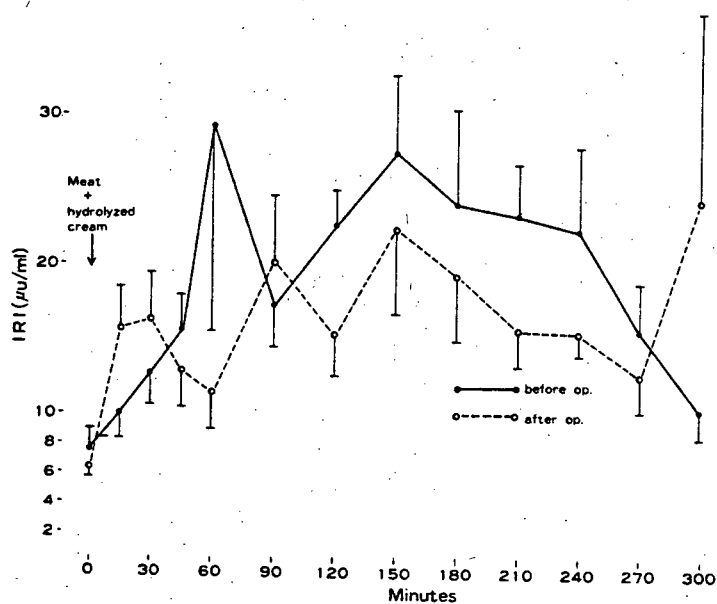
*Fig.* <sup>16</sup> *Serum glucose response to meat meal plus hydrolyzed cream before and after pancreatic duct ligation. Each point represents the mean and standard error of values for 4 dogs (8 experiments).*
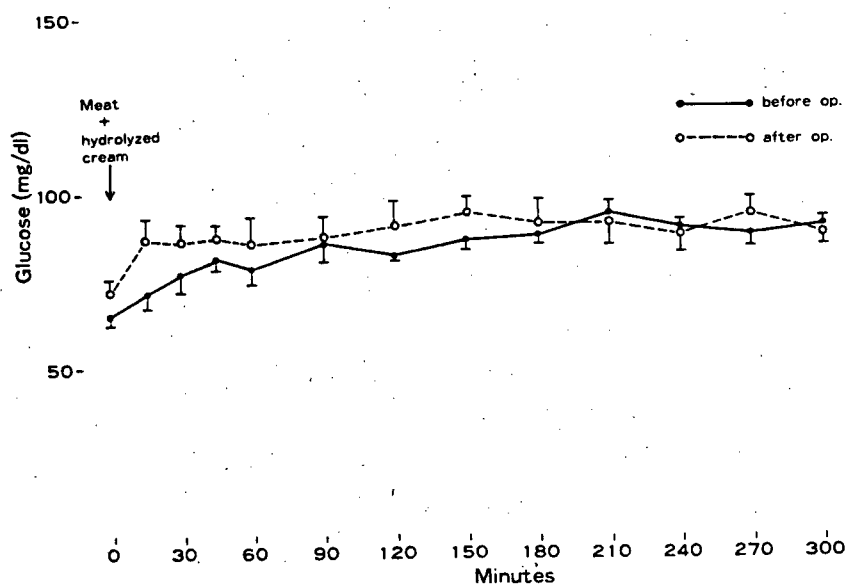
*Fig.* [17]  *Serum glucose response to i.v.glucose load before and after pancreatic duct ligation. Each point represents the mean and standard error of values for 4 dogs(8 experimetns). \*=p<0.05, \*\*=p<0.01, \*\*\*=p<0.005 (significant change compared with the control period).*
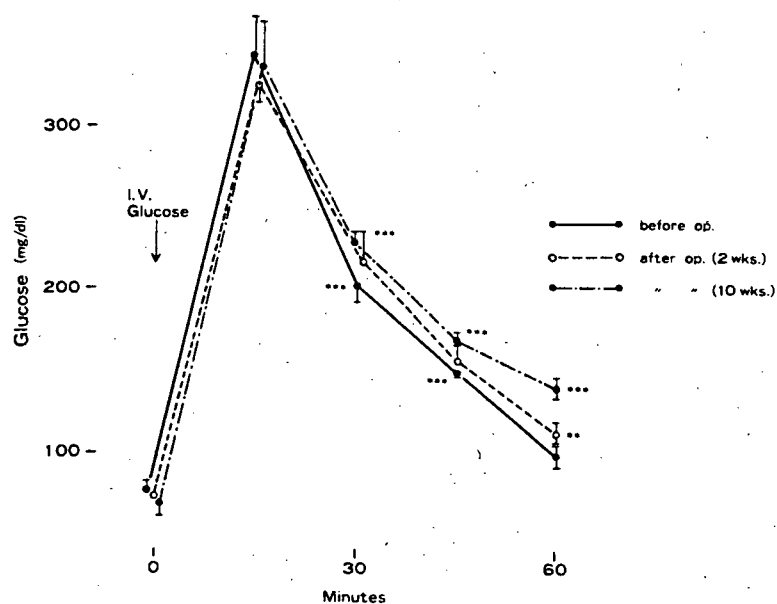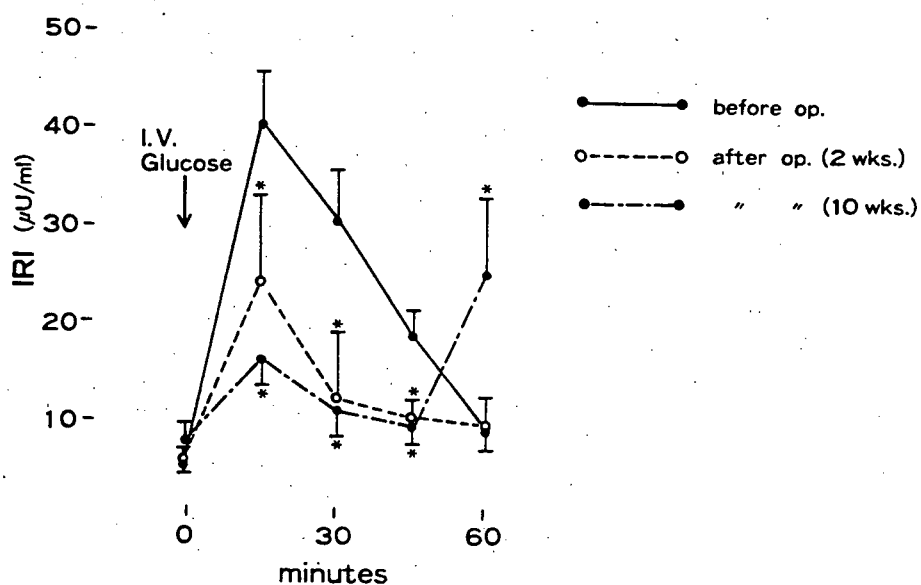
*Fig.* [18]    *Serum IRI response to i.v.glucose load before and after pancreatic duct ligation. Each point represents the mean and standard error of values for 4 dogs(8 experimetns). \*=p<0.05(significant change compared with the control period).*

Fig. 19 Serum glucose response to intragastric glucose load
before and after pancreatic duct ligation. Each point represents
the mean and standard error of values for 4 dogs(8 experiments).
*=p<0.05, **=p<0.01(significant change compared with the
control period).

Fig. 20 *Serum IRI response to intragastric glucose load before and after pancreatic duct ligation. Each point represents the mean and standard error of values for 4 dogs(8 experimetns).*
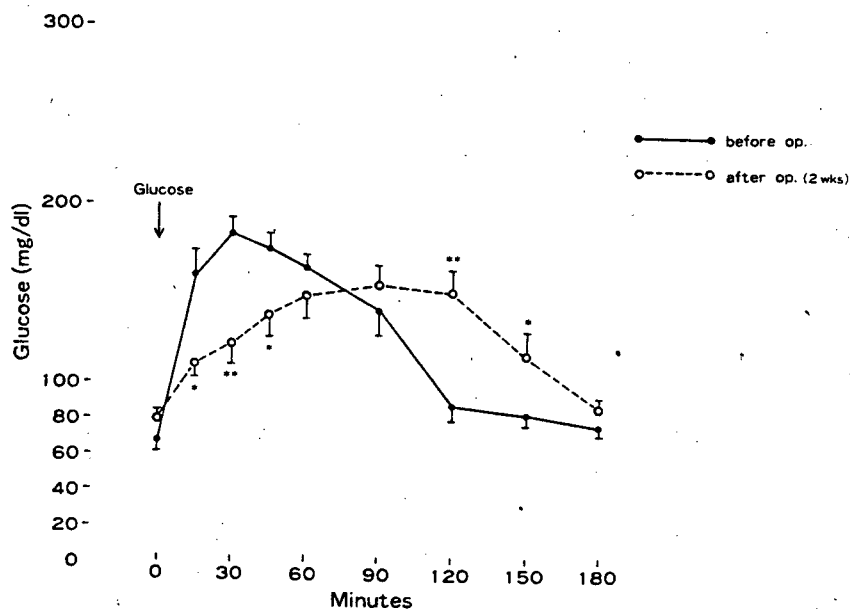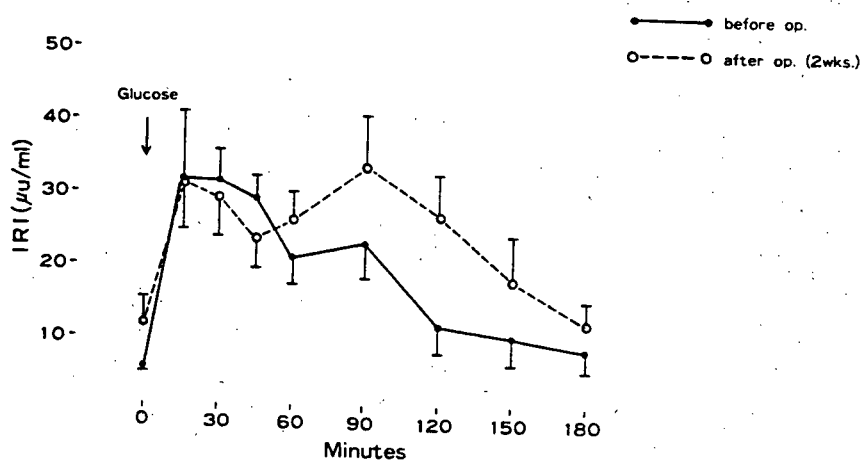
Fig. 21    *Serum GIP response to intragastric glucose load before and after pancreatic duct ligation. Each point represents the mean and standard error of values for 4 dogs (8 experiments).*
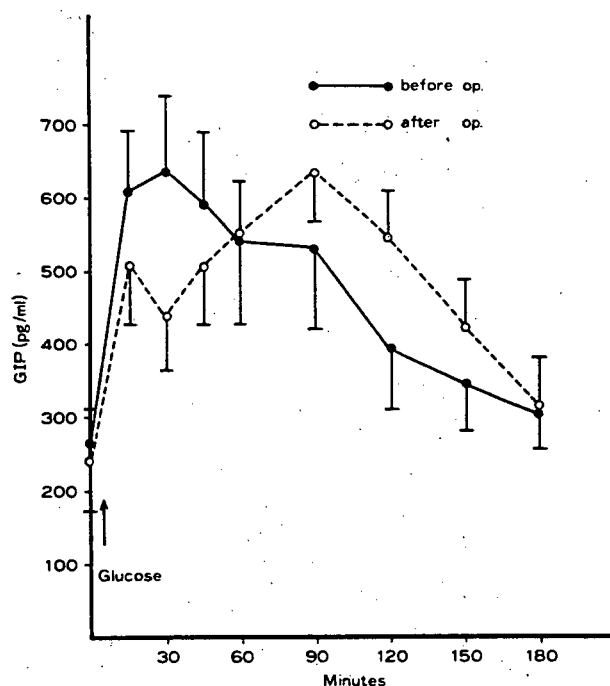
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APPENDIX

In order to ascertain the complete hydrolysis of cream by incubation with the digestive agent, gas chromatographic analysis was performed.

One hundred and twenty-five g of whipping cream (Silverwood Whipping Cream, Silverwood Dairies, Toronto, Canada. Ingredients: Fat 38.2 g, saturated fatty acids 21.4 g, oleic acid 1 g, protein 2.6 g, carbohydrate 4.2 g, calcium 0.1 g) was incubated with three capsules of Cotazymes (Organon Co., Toronto, Canada. Each capsule contains 800 units of pancreatic lipase) for three hours at 37° C.

After the incubation, released fatty acids were extracted with ether, crystalized as Ca-salt, and resolubilized as free fatty acid with concentrated HCl hydrolysis.

Boron trifluoride (BF3) methanol complex was used for the preparation of fatty acid methyl esters using the method of Metcalfe et al (Metcalfe L.D. and Schmitz A.A.: The rapid preparation of fatty acid esters for gas chromatographic analysis. Analytical Chem. 33: 363-364, 1961).

The hydrolyzed sample was put into the 50 ml of myer-flask cooled in an ice bath, added 7 ml of BF3 reagent, and boiled for two minutes; 5 ml of heptane was added and boiled for one munte; Heptane layer was raised up to the neck of the myer-flask with saturated aquous sodium chloride solution. Aliquot of heptane layer was taken into the sample bottle and

dried with disodium sulfate anhydride.

Gas chromatographic analysis was done using Hitachi 663 gas chromatograph (Hitachi Co., Tokyo).

Figures 1 to 5 show the chromatographic patterns and operating conditions. Figure 1 shows the pattern after 3-hour incubation without the digestive agent. Any fatty acid methyl ester peak cannot be seen. Figures 2, 3 and 4 illustrate single chromatographic patterns of methyl laurate, methyl palmitate and methyl stearate respectively as controls. Figure 5 shows the pattern of sample of 3-hour incubation with the digestive agent, and many peaks of fatty acid methyl esters which will correspond to the controls can be seen.
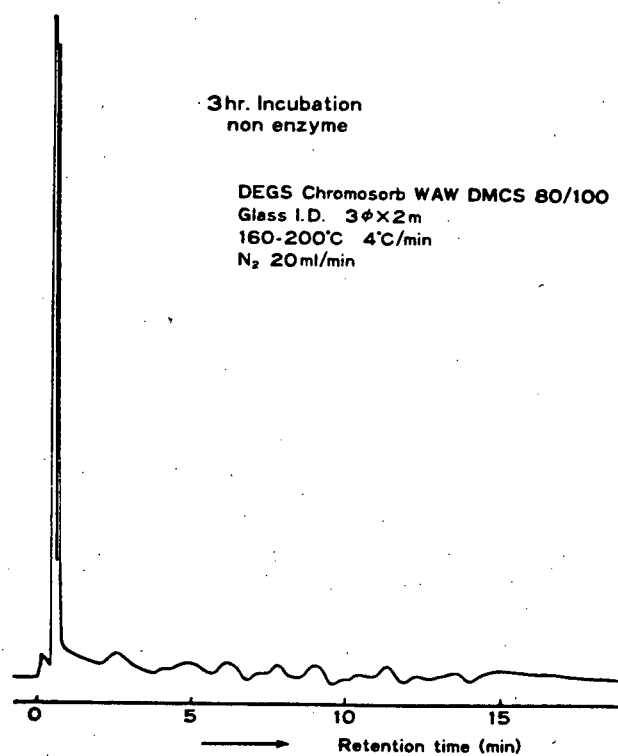
3hr. Incubation
non enzyme

DEGS Chromosorb WAW DMCS 80/100
Glass I.D.   3∅×2m
160-200°C   4°C/min
N₂  20ml/min

Retention time (min)

*Fig.1(for APPENDIX).   The chromatographic pattern of cream after 3-hr incubation at 37°C without the digestive agent.*
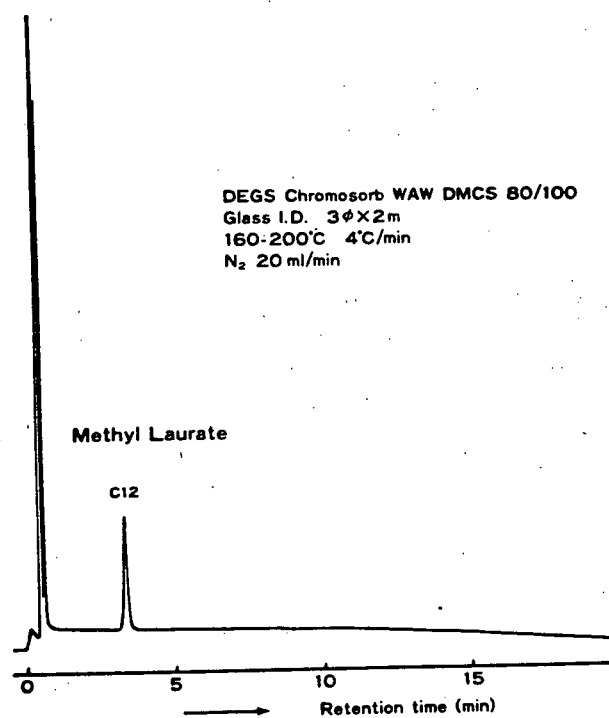
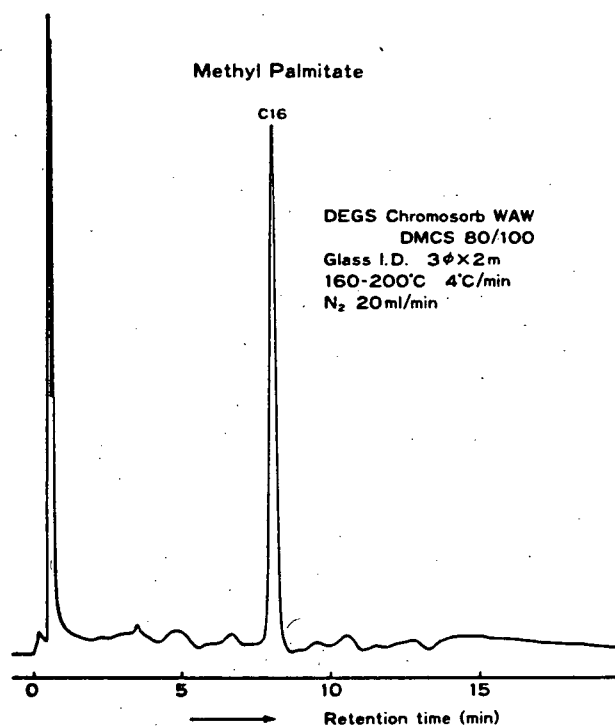Fig. 2(for APPENDIX).  The chromatographic pattern of
methyl laurate.

Fig. 3(for APPENDIX ).   The chromatographic pattern of
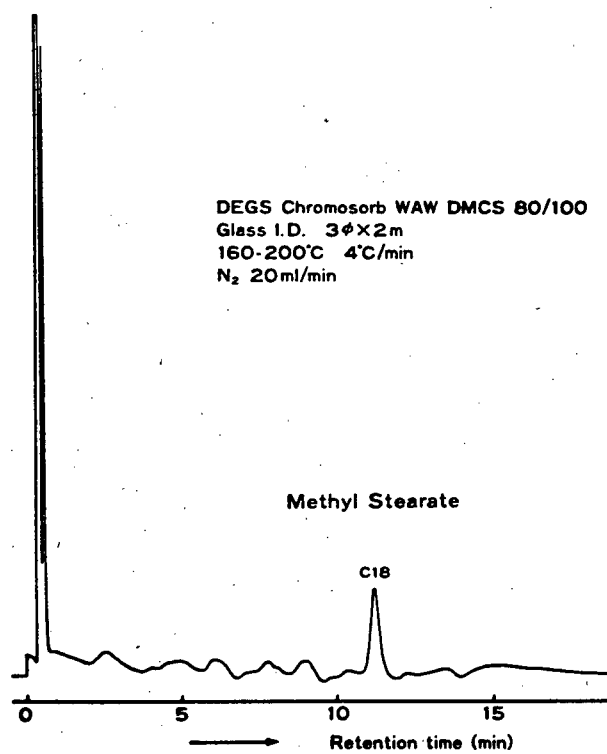methyl palmitate.

DEGS Chromosorb WAW DMCS 80/100
Glass I.D.  3φ×2m
160-200°C  4°C/min
N₂ 20ml/min

Methyl Stearate

C18

Retention time (min)

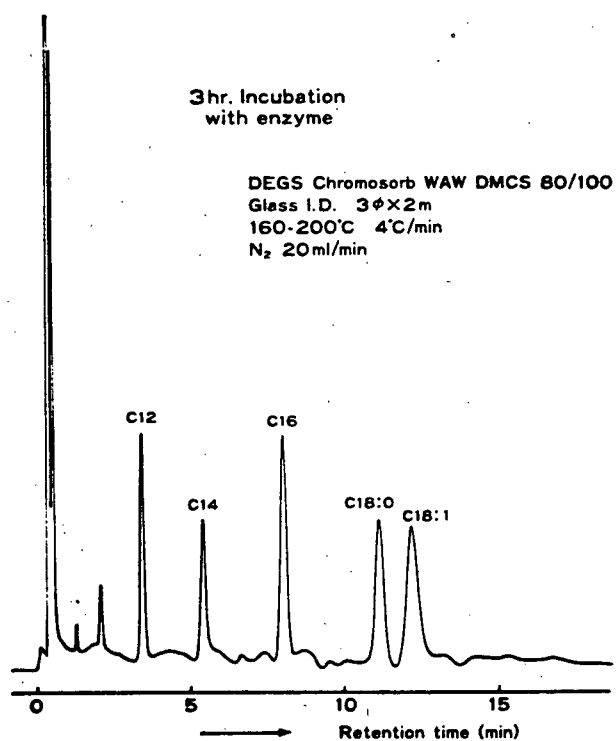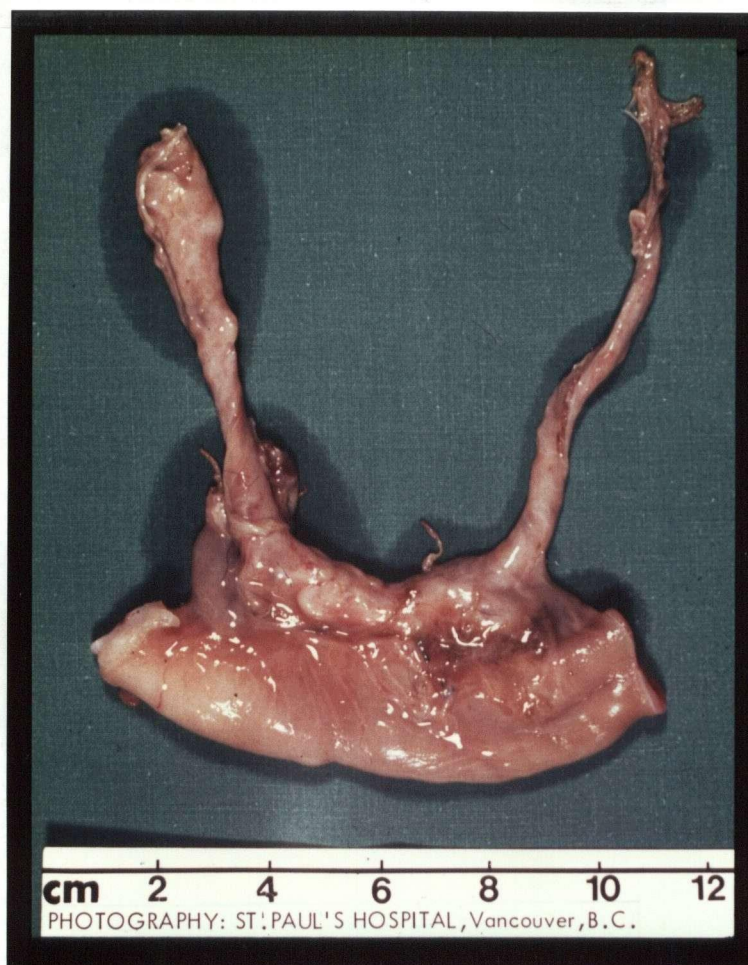*Fig. 4(for APPENDIX ).     The chromatographic pattern of*
*methyl stearate.*

Fig. 5(for APPENDIX ).    The chromatographic pattern of fatty acid methyl esters after 3-hr incubation at 37°C with the digestive agent.

PHOTOGRAPH: ST.PAUL'S HOSPITAL, Vancouver, B.C.

## PHOTOGRAPH I

Dog #4 post mortem specimen.
Duodenum and pancreatic ducts
showing atrophy of pancreas, but
no inflammation.

PAPERS WRITTEN:

1.    Stanisheff's operation for nephroptosis.   Operation (Japan) 25:661, 1971.

2.    A case of hydrops of the gallbladder due to non-calculous cystic duct obstruction.   Surgery (Japan) 38:427, 1976.

3.    Selective angiography in cancer of the pancreas at a resectable stage.   Am. J. Surg. 122:402, 1971.

4.    Surgical significance of anatomic variations of the hepatic artery. Am. J. Surg. 122:505, 1971.

5.    Zollinger-Ellison syndrome associated with parathyroid adenoma and ectopic gastric tissue in the lower esophageal mucosa.   Can. J. Surg.

6.    Peptic ulcer and glucose homeostasis:  I. Insulin, gastrin and glucagon responses to oral glucose and intravenous arginine in peptic ulcer patients.  Arch. Jap. Chir. 48:517, 1979.

7.    Relationship between GIP and insulin.  Surg. Ther. (Japan) 41:447, 1979.

8.    Negative feedback effect of insulin on the secretion of GIP.  Jap. J. Gastroenterol. 76:2432, 1979.

9.  A case of long term combined use of Neocarcinostatin and humanimmunoglobulin for colon cancer. Kiso-to-Rinsho 14:138, 1980.

10. The inhibitory effect of sulpiride in arginine-stimulated serum gastrin and growth hormone in normal subjects and peptic ulcer patients. Jap. J. Gastroenterol. 78:1363, 1981.

11. Peptic ulcer and glucose homeostasis: II. Insulin, gastrin and glucagon responses to oral and i.v. L-arginien in two groups of duodenal ulcer patients. Submitted to Gastroenterol. Jap.

PAPERS PRESENTED:

1.  Surgical significance of liver angiography (especially for liver cancer). The 8th Meeting of Japanese Society of Angiology. 1967.

2.  Simulation of splenic circulatory dynamics. The 7th Meeting of Japanese Society of Medical Electronics and Biological Engineering. 1968.

3.  Correlation of liver cancer and its blood supply. The 3rd Meeting of Japanese Society of Hepatology. 1967.

4.  Analysis of splenic and portal circulatory dynamics. The 9th Meeting of Japanese Society of Angiology. 1968.

5.  Analysis of splenic and portal circulation using superselective radioisotope injection to splenic artery. The 9th Meeting of Japanese Society of Nuclear Medicine. 1969.

6.  Angioscanography of liver cancer. Kyoto Surgical Congress. 1969.

7.  Hepatoma of infant. Kyoto Surgical Congress. 1969.

8.  Experience of modified Stanischeff's operation for nephroptosis. Okayama Surgical Association. 1970.

9.  A case of hydrops of the gallbladder due to noncalculous cystic duct obstruction. Kinki Surgical Association. 1972.

10. Intraoperative exploration of the gastric mucosal change. Kinki Surgical Association. 1973.

11. Traumatic urachal cyst of the kidney. Kinki Surgical Association. 1977.

12. Amylase-creatinine clearance ratio following intravenous injection of pancreozymin in chronic pancreatitis. Kinki Surgical Association. 1977.

13. Peptic ulcer and glucose homeostasis. Kinki Surgical Association. 1979.

14. Hiatus hernia associated with peptic ulcer. Kinki Surgical Association. 1979.

15. Radical operation for intrahepatic stones. Kinki Surgical Association. 1978.

16. The negative feedback control of GIP by insulin. The 20th Meeting of Japanese Gastroenterology Association. 1978.

17. GIP following ligation of the pancreatic duct in dogs. The 14th Meeting of Japanese Gastroenterological Surgery Association. 1979.

18.  Intravenous arginine, and oral glucose stimulated insulin, gastrin and glucagon in peptic ulcer patients. The 22nd Spring Meeting of Japanese Gastroenterology Association. 1979.

19.  Post-splenectomy thrombocythemia. Japan Clinical Hematology Association. 1979.

20.  Serum CEA levels after mumps virus vaccine injection for colon cancer. Kinki Surgical Association. 1979.

21.  Perforated small intestinal ulcer. Kyoto Emergency Treatment Association. 1979.

22.  Serum gastrin, insulin and glucagon in response to intravenous arginine in peptic ulcer patients. The 15th Meeting of Japanese Gastroenterological Surgery Association. 1980.

23.  The suppressive effect of sulpiride on arginine-stimulated gastrin and growth hormone. The 66th Meeting of Japanese Gastroenterological Association. 1980.

24.  Disseminated intravascular coagulation associated with acute obstructive supprative cholangitis. Kinki Surgical Association. 1980.

25. Treatment of colon cancer with Neocarcinostatin and human immunoglobulin.  Kyoto Cancer Research Association.  1980.

26. Abdominal trauma.  Kyoto Medical Association.  1980.

27. Treatment of peptic ulcer.  Kyoto Medical Association.  1980.