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# Plasma Glucagon after Total Resection of the Pancreas in Man (39435)

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Although it has been reported that in dogs plasma glucagon not only does not disappear after pancreatectomy (1–3) but may actually increase if the animals receive no insulin treatment (4, 5), little is known about similar changes in man (6). Recently, we carried out serial measurements of plasma pancreatic glucagon and of glucagon-like immunoreactive materials during and after total resection of the pancreas in a patient with chronic calcified pancreatitis. The response of plasma pancreatic glucagon to arginine infusion was also examined.

*Case report.* Our patient was a 62-year-old man who did not drink alcoholic beverages and who underwent total resection of the pancreas, the duodenum, and the distal half of the stomach on July 1, 1974. Reconstruction of the alimentary tract was done as shown in Fig. 1. Severe pain and intermittent fever with leukocytosis had been present over a 5-year period. Conservative treatment had been ineffective and the patient had lost weight due to anorexia caused by frequent attacks of pain. Analgesic injections had been given three to five times daily for several months prior to surgery. Insulin administration had been discontinued following a decrease in blood glucose with loss of appetite and poor dietary intake. At the time of operation the patient weighed 40 kg.

The operative procedure was uneventful. The resected pancreas weighed 40 g and was completely calcified with multiple cystic formations in the ducts. Histological examination revealed fairly well preserved islets of Langerhans and markedly reduced acinar tissue.

Just before the final phase of pancreatectomy, infusion of regular insulin and glucose was started. The infusion of insulin was replaced by multiple subcutaneous injections of regular insulin from the 4th postoperative day on. The postoperative course of this patient has been uneventful up to the time of this writing, 16 months after the surgery. The preoperative complaints have disappeared and he has gained 3 kg.

Serial measurements of pancreatic glucagon and of glucagon-like immunoreactive materials were made during and after the operation until the 10th postoperative day.

*Sampling.* Peripheral venous blood was collected into heparinized syringes, plasma was separated immediately and stored at −20° until ths time of assay. Aprotinin[2] (1000 kIU/ml) was added to the plasma before refrigeration.

*Assays.* Plasma levels of glucagon (IRG) were measured by a single antibody radioimmunoassay (7) using an antiserum (AGS 30K), prepared in the laboratory of Dr. Roger Unger, Dallas, and found to be specific for pancreatic glucagon (8, 9). "True glucagon" (PG) values were corrected according to Weir's method (10), except that cellulose powder was used for the preparation of glucagon-free plasma (9). The assay system for PG in this study is capable of detecting changes of 25 pg/ml with 95% confidence. Fasting plasma levels of IRG and PG in healthy subjects were 223 ± 154 pg/ml (mean ± 1 SD, $n = 14$) and 37 ± 23 pg/ml (mean ± 1 SD, $n = 14$), respectively (9).

Plasma levels of glucagon-like immunoreactive materials (GLI) were also measured by a single antibody radioimmunoassay using AGS 10, prepared in the laboratory of Dr. P. P. Foà and kindly provided by Drs. K. Shima and T. Sugase. This antiserum cross-reacts with crude GLI prepared from the mucosa of the small intestine (11).

*Results.* As shown in Fig. 2, plasma IRG decreased progressively up to the end of the

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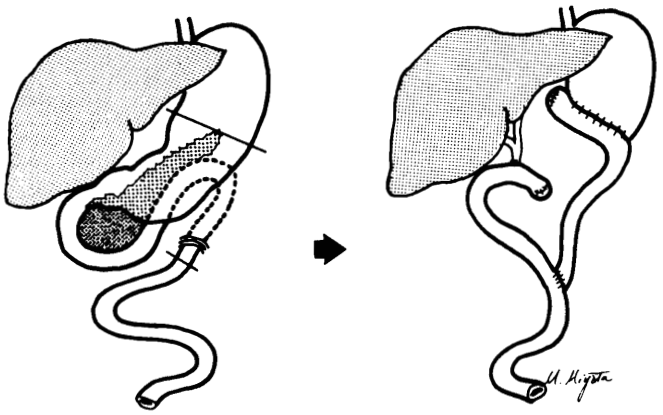

FIG. 1. Diagram of the operative procedure for total resection of the pancreas.

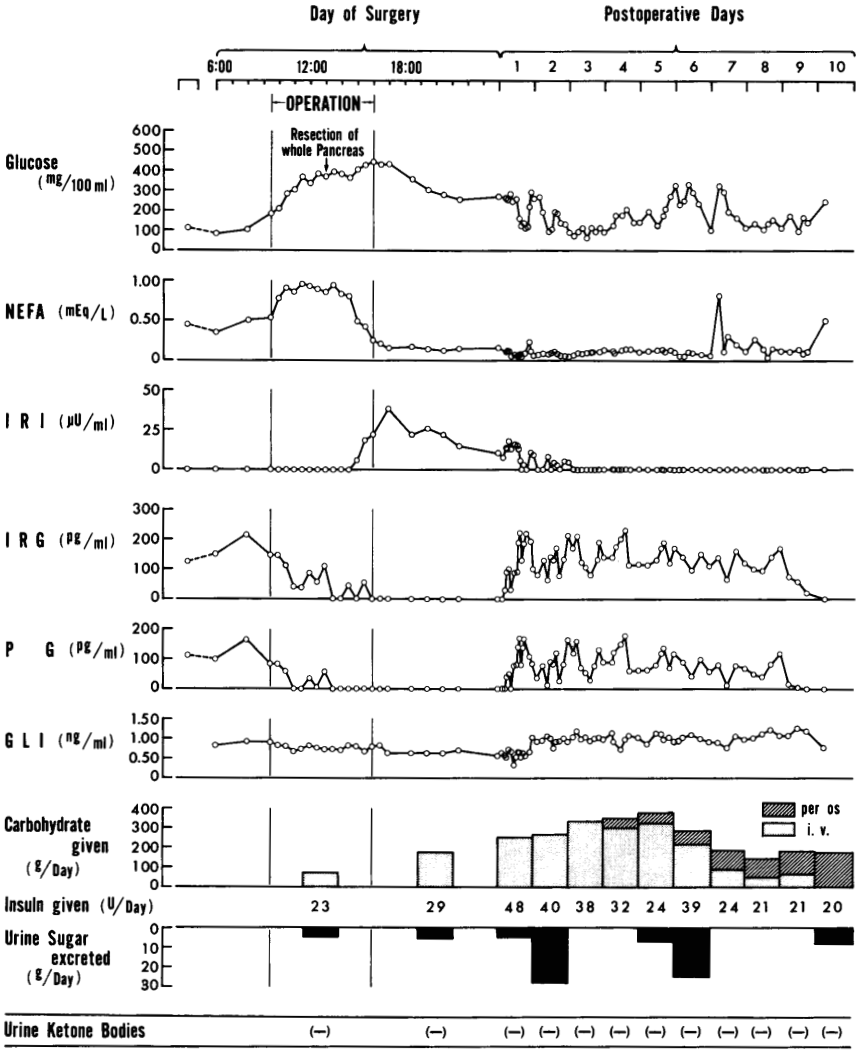


FIG. 2. Changes in plasma levels of glucose, nonesterified fatty acids (NEFA), insulin (IRI), glucagon (IRG), "true glucagon" (PG), and glucagon-like immunoreactive materials (GLI) during and after total resection of the pancreas.

operation and became undetectable until the first postoperative day. Plasma PG also decreased after the start of the operation and became undetectable within 30 min following the resection of the entire pancreas. On the first postoperative day, about 18 hr after total pancreatectomy, PG was again detectable in the blood and fluctuated considerably until the ninth postoperative day when it disappeared again.

Plasma levels of GLI gradually decreased after the start of the operation and during the second postoperative day, increasing abruptly thereafter, and remaining elevated until the ninth postoperative day. This abrupt increment of GLI coincided with the resumption of peristalsis after surgery.

As shown in Fig. 3, plasma IRG levels did not change in the blood following arginine infusion, even though the expected rise in growth hormone level was noted. PG did not appear in the blood during the infusion.

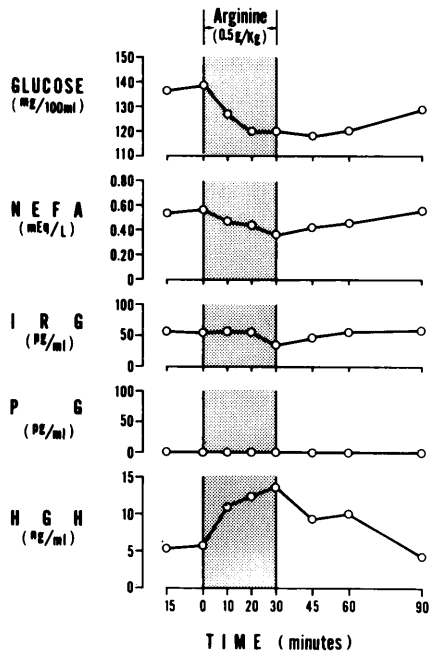


FIG. 3. Response of plasma glucose, nonesterified fatty acids (NEFA), glucagon (IRG), "true glucagon" (PG), and growth hormone (HGH) to arginine infusion during the fourteenth postoperative week. This examination was carried out after an overnight fast and 18 hr following the last injection of insulin. All values of "true glucagon" during the test were within the limits observed in the patient's plasma after adsorption on cellulose powder ("glucagon-free plasma").

*Discussion.* During surgery, independent observers confirmed that the pancreas had indeed been wholly resected and that accessory or ectopic pancreatic tissue could not be found in the abdomen. Thus, given a half-life of glucagon of about 4 min (12) there should have been no detectable PG in the blood of this patient after surgery. Nevertheless, variable amounts of PG were found between the first and ninth postoperative day. Since the fluctuation of PG did not parallel those of GLI and since AGS 30K cross-reacts minimally with GLI, the results strongly suggest that the immunoreactive material detected in the plasma after total pancreatectomy in this patient was not GLI. Similar findings have been reported in dogs (2, 3). Furthermore, in depancreatized dogs, the plasma level of PG increased with the withdrawal of insulin and was restored to almost normal values following the resumption of insulin treatment (4, 5). In our patient, plasma levels of glucose and nonesterified fatty acids (NEFA) were satisfactorily controlled by insulin, and ketone bodies were not detectable in the urine. Perhaps because of this, the maximum level of immunoreactive glucagon after total pancreatectomy was only twice the postoperative fasting level. On the other hand, plasma insulin (IRI) was not measurable except for the period when large doses of regular insulin were given shortly after pancreatectomy.

From the tenth postoperative day on, PG was not detectable in the blood of this patient and, during the fourteenth postoperative week, none appeared following arginine infusion. During the infusion, plasma glucose and NEFA decreased, probably due to the absence of glucagon. This lack of glucagon response is compatible with the observations of other investigators (6) and with our findings in another depancreatized patient. This 68-year-old male was admitted to the hospital, complaining of general weakness, 11 weeks after total resection of the pancreas for carcinoma. On admission (25 hr following the last injection of NPN insulin), the blood sugar level was 334 mg/100 ml, glucose (++) and ketone bodies (++) were detected in the urine. No detectable

amounts of IRG and PG appeared in the plasma during arginine infusion. Thus, in depancreatized humans, ketosis does not appear to require the presence of measurable amounts of plasma glucagon. These observations on the absence of plasma glucagon response to arginine in patients after total pancreatectomy are compatible with the results obtained in well-insulinized depancreatized dogs (6), although not in untreated depancreatized animals (1, 2, 13).

Several possibilities may be considered to explain our findings: (i) release of PG from extrapancreatic tissue, (ii) appearance of unknown substances which cross-react with AGS specific for pancreatic glucagon, (iii) production of unknown metabolites which influence the radioimmunoassay. The most probable explanation appears to be the first one, since there is evidence that a pancreatic glucagon-like substance may be found in the mucosa of the gastric fundus and the duodenum (14), in the kidney (15, 16), and in the submaxillary gland (16–18). Indeed, the proximal half of the stomach was preserved in our patient. The facts that no plasma PG was detectable after the tenth postoperative day and that arginine infusion could not evoke a response may be due to insulin treatment, a procedure known to suppress glucagon secretion (5). It can be also speculated that, due to low levels of PG in the portal blood, insufficient amounts of this hormone may have escaped the liver to be detectable in the posthepatic blood.

The data described in this paper suggest that, also in man, "true" glucagon originates in organs other than the pancreas.

*Summary*. Serial measurements of plasma "true glucagon" (PG) and of glucagon-like immunoreactive materials (GLI) were carried out during and after total resection of the pancreas in a 62-year-old man with calcified pancreatitis. The postoperative course of this patient was uneventful and diabetes was well controlled. PG disappeared from the blood within 30 min after resection of the pancreas. In spite of the evidence that no pancreatic tissue was present in the abdomen, PG was detected again in the blood from 18 hr after total pancreatectomy until the ninth postoperative day. However, plasma PG did not rise following infusion of arginine during the fourteenth postoperative week. After an initial decrease, plasma GLI rose abruptly on the second postoperative day and remained elevated thereafter. The fluctuations of plasma PG and GLI were not parallel.

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