ENHANCEMENT OF PANCREATIC CONCENTRATION OF ^{75}Se-SELENOMETHIONINE

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In order to improve the reliability of pancreas scanning, particularly the elimination of falsely abnormal scans, we have tested the effects of various stimulatory regimens upon the uptake of ^{75}Se-selenomethionine by the rat pancreas. Urecholine proved to have a mild stimulatory effect while the parasympatholytic agent propantheline bromide had a reverse action. The combination of urecholine, followed by pancreazymin, caused a marked enhancement of tracer uptake.

This combined regimen has been further evaluated in human subjects with encouraging results. Falsely abnormal results have been largely eliminated, and side effects have been quite tolerable. It is proposed that parasympathetic stimulation is required for optimal pancreatic function.

Pancreatic photoscanning with ^{75}Se-selenomethionine has proven to be only marginally reliable. One of the main problems has been failure to visualize glands subsequently shown to be normal. The incidence of this may be as high as 30% (*1*) and no explanation for it has been determined.

In addition to a search for a better scanning agent and improved instrumentation techniques, efforts to make this procedure more reliable have been directed toward pharmacologic enhancement of tracer concentration by the pancreas. These have been based either on means of increasing enzyme production (and therefore tracer incorporation) by using agents such as pancreozymin (*2*) or delaying gland emptying with anticholinergic agents or morphine. Neither of these techniques nor preparation by various feeding or fasting regimens (*3,4*) has proven generally successful and none is in widespread use.

In lieu of a tracer superior to selenomethionine, we have evaluated several other methods of pharmacologic enhancement.

ANIMAL STUDIES

Methods. Female Wistar rats, 150–225 gm, fed a normal laboratory diet, were used. Feeding was not interrupted for the study. Drugs and tracer were administered intravenously through the tail vein or intraperitoneally. Selenium-75-selenomethionine, approximately 4 μCi, was administered following 10–15 min each drug used and the animals killed 30 min later. Portions of liver, pancreas, small bowel, and diaphragm were removed, washed and blotted dry, weighed, and counted in a Searle Radiographics auto-gamma well counter.

Tracer concentration was expressed as the ratio of radioactivity in pancreas, liver, and bowel to general body background radioactivity (approximated by diaphragm muscle).

Agents employed included pitressin, 3.0 units/kg body wt, i.p., two animals; glucagon 1.0 mg/kg body wt, i.v., three animals; bethanechol chloride (urecholine) 1.0 mg/kg body wt, i.v., three animals; pancreozymin-CCK* 4.0–8.0 units/kg, i.v., four animals; urecholine plus pancreozymin in same doses as above, five animals; and propantheline bromide (probanthine) 3.0 mg/kg body wt, i.v., three animals. In addition, four animals given only ^{75}Se-selenomethionine served as controls.

Results. The individual and mean results of the studies are graphically presented in Fig. 1. Pitressin decreased and glucagon did not affect pancreatic tracer concentration. Urecholine caused a consistent ($p < 0.02$ Student's t-test) although mild enhancement of tracer uptake amounting to an increase of

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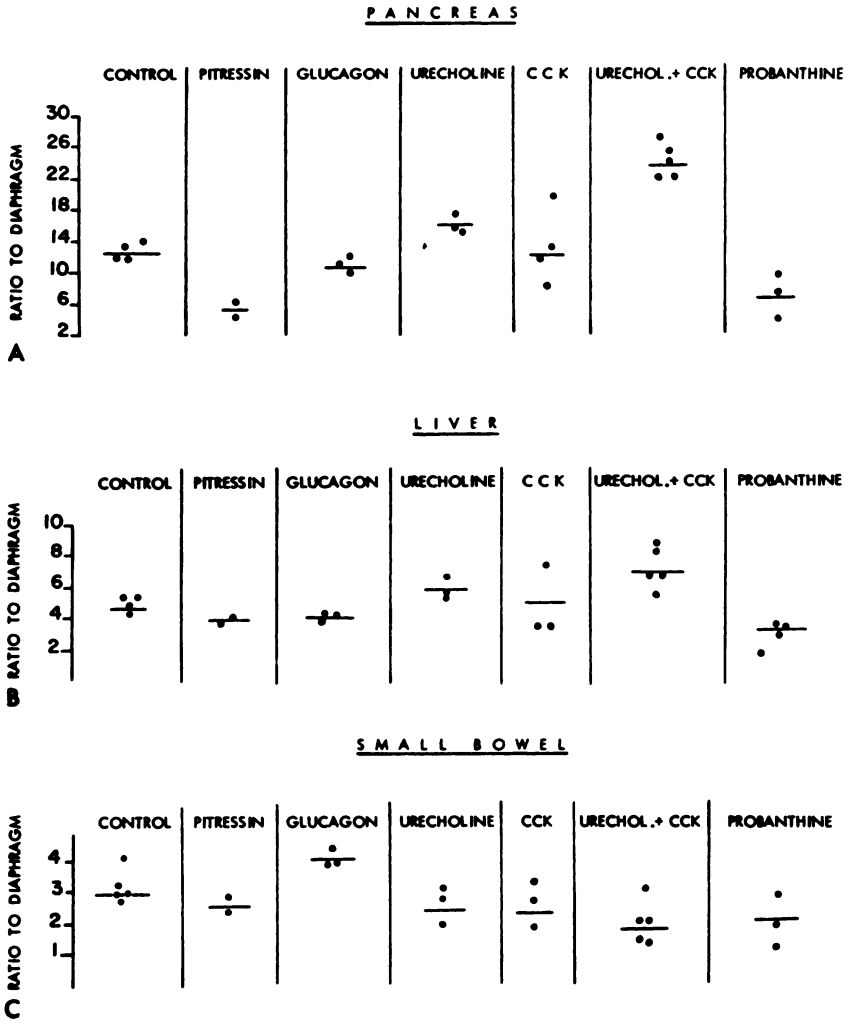


FIG. 1. Results of various stimulatory regimens on tracer uptake in pancreas (A), liver (B), and small bowel (C).

approximately 33% over control values. Pancreozymin was somewhat variable in its effect but in general there was no significant difference from control values ($p \geqq 0.8$). The results of giving 4.0 units/kg could not be distinguished from 8.0 units.

The combination of urecholine, 1.0 mg/kg, followed in 10 min by pancreozymin-CCK or 4.0 or 8.0 units/kg, significantly ($p < 0.01$) and consistently increased tracer accumulation in the pancreas, as compared with control levels, by about 100%. In contrast, pro-banthine, 3.0 mg/kg, significantly (<0.05) reduced pancreatic tracer concentration.

The effects of these drug regimens on the liver and bowel generally paralleled results in the pancreas but did not vary so widely (Figs. 1B and C).

PATIENT STUDIES

Methods. Fifteen patients have been studied so far using a stimulation technique based on the preceding work. This consists of 5 mg urecholine administered subcutaneously followed in 15 min by 1 unit/kg pancreozymin instilled intravenously over a 3–4-min period. The usual scanning dose of ^{75}Se-selenomethionine (3 μCi/kg) is given 1 min after the conclusion of this instillation and imaging is begun immediately thereafter on a Pho/Gamma scintillation camera.

The medium-energy collimator is used and the patient is positioned supine with about a 10-deg right rotation. Fifty thousand count images, requiring about 8 min each, were obtained serially.

Two patients had acute pancreatitis in an early subsiding phase, two had severe chronic pancreatitis with malabsorption, and one had a pseudocyst demonstrable by ultrasonography. The other patients had no known pancreatic disease but were examined for complaints of abdominal pain or suspected occult carcinoma.

Results. The pancreas is generally well visualized on the first image, improving on the next one or two images primarily due to clearing of the background. After this, the image worsens due to rapid excretion of tracer from the gland. We have defined fair visualization as demonstration of all parts of the pancreas but poorly defined; good visualization means good definition whereas excellent visualization indi-

cates pancreatic activity equal to or superior to that in the liver.

As shown in Table 1, the pancreas was readily identified in almost all cases except one with severe chronic pancreatitis.

Visualization was good to excellent in all cases with a normal pancreas. No pancreatic disease has been found in any of these individuals during 6 months of followup. Focal defects (one pseudocyst and one area of severe chronic pancreatitis) were identified in two individuals (Fig. 2).

Side effects, while not uncommon, were generally very mild consisting of slight cramping or nausea or both during administration of pancreozymin. One patient with a very recent episode of acute pancreatitis had a flare-up of pain which subsided spontaneously within 10 min.

DISCUSSION

Although it is far from ideal, ^{75}Se-selenomethionine has remained the standard pancreatic scanning agent since its introduction over 10 years ago (*5*). In the absence of an improved agent, many efforts have been made to increase pancreatic concentration of selenomethionine. These have attempted either to increase the initial uptake of tracer or to prolong its retention within the organ and we have in general employed the same rationale.

Glucagon was used because it has been reported to be a useful agent in acute pancreatitis, presumably by interfering with release of pancreatic digestive enzymes (*6*). In the present study, glucagon had no significant effect on pancreatic tracer concentration.

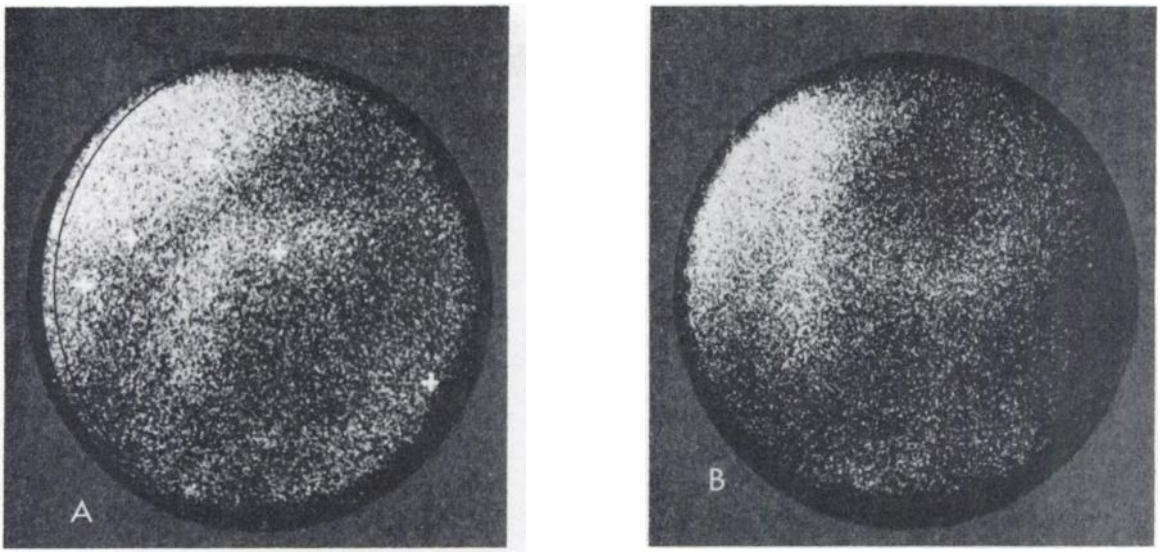
Pitressin, on the other hand, is used clinically in treatment of bleeding esophageal varices because it causes a reduction in portal blood flow. It was hoped that this would result in reduced concentration of tracer by the liver and thus decrease interference with visualization of the pancreas by scanning. However, tracer concentration in all three organs studied was reduced, presumably because circulation throughout the entire splanchnic bed including the pancreas was reduced.

Hansson found pilocarpine to speed up both the uptake and release of labeled methionine by the mouse pancreas but did not describe any absolute increase in its concentration (*7*). However, urecholine has been shown to enhance incorporation of ^{32}P into pancreatic phospholipids in rats previously fed a high ethanol-content diet, bringing them back to control levels although it had little further effect on controls (*8*). The same phenomenon occurred in animals subjected to vagotomy. Presumably therefore, the ethanol had a vagolytic effect and some vagal "tonus" is necessary for optimal pancreatic function.

This may well explain the increased incidence of nonvisualization of a normal pancreas in alcoholic patients, a phenomenon which has previously been attributed to a coexisting subclinical pancreatitis. A similar high incidence of nonvisualization exists in individuals previously subjected to gastrectomy or vagotomy (*2,9*). In addition, the use of anticholinergic agents in treatment of presumed cases of acute pancreatitis may also hinder visualization upon attempted scanning. Certainly, our data confirmed a

TABLE 1. CLINICAL RESULTS OF PANCREAS SCANNING USING A STIMULATORY REGIMEN

Patient	Diagnosis	Scan result	Side effects
HA	Chronic relapsing pancreatitis	Gland well seen except for tail	Mild cramping
EC	Mild pancreatitis, alcoholic	Fair to good visualization	Moderate cramping, bowel movement
DM	Severe pancreatitis, 3 mos previously	Fair to good visualization	None
CK	Moderately severe pancreatitis, 1 wk previously	Good, except patchiness in head	Abdominal pain as during pancreatitis; resolved spontaneously in 10 min
GB	Pancreatic pseudocyst on ultrasonic B scan	Excellent visualization, defect in central portion	None
CC	Recent moderate pancreatitis	Good visualization	None
WS	Ascites	Good visualization	None
SY	Stomal ulcer	Good visualization	Mild cramping
WP	Suspected carcinoma	Excellent visualization	None
GL	Gastric ulcer	Excellent visualization	Mild cramping, slight nausea
HM	Chronic relapsing pancreatitis	Good visualization except patchy head	None
LF	Probable esophagitis	Excellent visualization	None
GV	Malabsorption	Excellent visualization	Mild nausea and cramping
LK	Possible occult carcinoma	Good visualization	None
HH	Carcinoma of pancreas	Good visualization of head and tail, absence of tracer midportion	Nausea, bowel movement



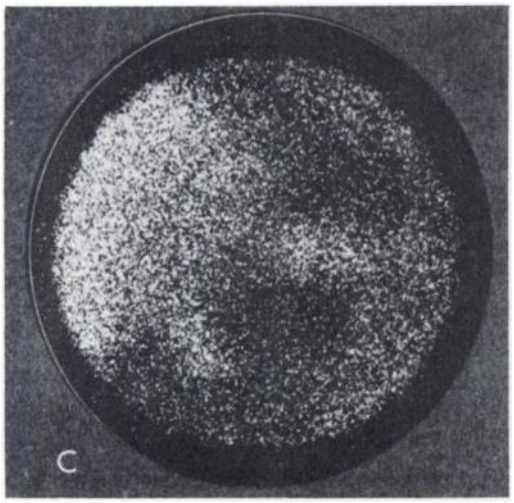


FIG. 2. (A) Normal pancreatic scintiphoto, (B) chronic pancreatitis, and (C) is pancreatic pseudocyst—note apparent thinning of inferior border in midportion of gland.

marked reduction in pancreatic tracer concentration in the rats pretreated with pro-banthine.

Urecholine alone caused only a modest enhancement of pancreatic tracer concentration in our animals, which had been on a normal diet. This seemed to be part of a more generalized splanchnic effect since hepatic and small bowel tracer concentrations were also increased. Urecholine alone, therefore, appears to offer only mild advantage with regard to pancreas scanning in general although in the circumstances indicated above, its use may be more critical.

Pancreozymin-CCK alone generally had little effect although results here were quite variable. Similar results were obtained by Kupic, et al in dogs using pancreozymin-CCK and secretin individually or in combination (*10*). However, the combination of urecholine followed by pancreozymin-CCK appeared to act synergistically and consistently resulted in a quite significant rise in pancreatic tracer concentration. This was out of proportion to the milder increments in hepatic and bowel uptake and was therefore thought likely to prove quite useful in organ scanning (*11*).

Our clinical experience has confirmed this. Nonvisualization of normal glands has not occurred and even acutely inflamed glands were visualized, although not so plainly. Only chronic destructive changes or mass lesions resulted in nonvisualization; thus the false-positive scan at least has been circumvented.

Side effects were quite tolerable and even acute pancreatitis appears to present no more than a relative contraindication to this stimulatory regimen. Only bowel obstruction would constitute an absolute contraindication since both urecholine and pancreozymin enhance bowel motility. Their stimulation of pancreatic tracer uptake is probably accomplished by a combination of enhanced blood flow and enzyme synthesis (*11*).

ADDENDUM

Since submission of this manuscript, an additional 35 patients have been studied. Two cases of pancreatic carcinoma and one of severe chronic pancreatitis have been discovered due to nonvisualization of all or a portion of the gland. No false-positive studies have occurred despite a fairly heavy incidence of alcoholism and various degrees of pancreatic inflammatory conditions in this population. Side effects continue to be quite mild and well tolerated.

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