

# Hyperamylasaemia after duodenoscopy and retrograde cholangiopancreatography

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**SUMMARY** The salivary and pancreatic isoamylases of serum were determined separately in 234 cases of duodenoscopy and retrograde cholangiopancreatography. Successful pancreatic opacification was associated with pathologically high pancreatic serum amylase activities in 60% of the cases. Extensive opacification was associated with large increases of pancreatic serum isoamylases, the maximal rise recorded was 40 times the initial value. In spite of these striking chemical events only two patients developed clinical acute pancreatitis. There were some variations in pancreatic opacification and in the elevation of pancreatic serum amylase which seemed to depend upon the particular contrast material used. A rise of the salivary serum isoamylases caused pathologically high total serum amylase activities in 7% of the cases. High levels of pancreatic serum isoamylase activity before the time of examination did not result in any different pattern of hyperamylasaemia.

Radiographic visualization of the pancreatic and bile duct systems, endoscopic retrograde cholangiopancreatography (ERCP) has been used with increasing frequency in recent years. Successful filling of the pancreatic duct system has been reported to result in a temporary rise of total serum amylase activity in 20 to 70% of cases. Attacks of acute pancreatitis have been observed with a frequency which varies between 1 and 17% (Kasugai *et al.*, 1971; Cotton, 1972; Kasugai *et al.*, 1972; Blackwood *et al.*, 1973; Ruppin *et al.*, 1974), and fatalities have occurred (Amman *et al.*, 1973; Ruppin *et al.*, 1974). Total urinary amylase output has been reported to increase after esophagogastrosocopy even without attempts to cannulate the ampulla of Vater (Blackwood *et al.*, 1973), and swelling of the submaxillary salivary gland has occurred after peroral endoscopy (Slaughter and Boyce, 1969).

Total serum and urinary amylase activities include pancreatic and salivary components. Thus, it seemed important to study the pancreatic and salivary isoamylases separately in a consecutive series of patients undergoing ERCP to determine the frequency with which amylase activities are altered by the procedure, the magnitude of the alterations that occur, and the influence of the other factors.

## Methods

The material includes observations from a total of 234 consecutive endoscopic examinations that were performed on 219 patients because of suspected duodenal, pancreatic, or hepatic disease.

The activity of the pancreatic isoamylases in serum was normal in 203 cases and it was pathologically increased before starting the examination in 31 cases. Duodenoscopy with inspection of Vater's ampulla but without cannulation was performed in 18 of the examinations. In 17 examinations Vater's ampulla was localized but attempts to cannulate it were unsuccessful, although the papilla was picked upon repeatedly with the cannula tip. The bile system was selectively cannulated in 25 cases and the pancreatic duct system was cannulated with or without simultaneous opacification of the bile system in the remaining 174 cases.

In patients with initially normal pancreatic serum isoamylase activity, the behaviour of the pancreatic isoamylase pattern of serum after the endoscopic examination was studied in relation to the following factors: degree of contrast filling of duct system, contrast medium used, pain during injection, and pancreatic morphology. The pancreatic serum isoamylase was also studied in patients with initially increased activity, as were changes of the salivary isoamylase pattern in serum after the endoscopic examination.

The instrument used was an Olympus Duodeno-

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fiberscope JF type B or B2 furnished with a Teflon catheter (1.7 mm OD, 1.0 mm ID). The cannula was inserted 3-15 (30) mm inside the opening of the papilla before manual injection of the contrast medium by means of a hand-held 20 ml syringe. The contrast injection was performed under fluoroscopic control. Before examination the patients had fasted for seven to 10 hours. The patients were given 5-20 (30) mg diazepam (Valium, Hoffman-La Roche, Basel, Switzerland) and 40-80 (160) mg hyoscine n-butyl bromide (Buscopan, Boehringer, Ingelheim, German Federal Republic) intravenously before endoscopy. For radiographic opacification of the pancreatic duct system sodium and methyl-glucamine diatrizoate (Urografin 60%, Schering AG, Berlin/Bergkamen, German Federal Republic) was used in 71 and sodium, calcium, magnesium, and methyl-glucamine metrizoate (Isopaque 350, Nyegaard, Oslo, Norway) was used in 80 of the 151 pancreatograms obtained in patients with initially normal pancreatic serum amylase activity. In the remaining examinations either contrast medium was used.

Blood samples were drawn for amylase determinations immediately before and immediately after

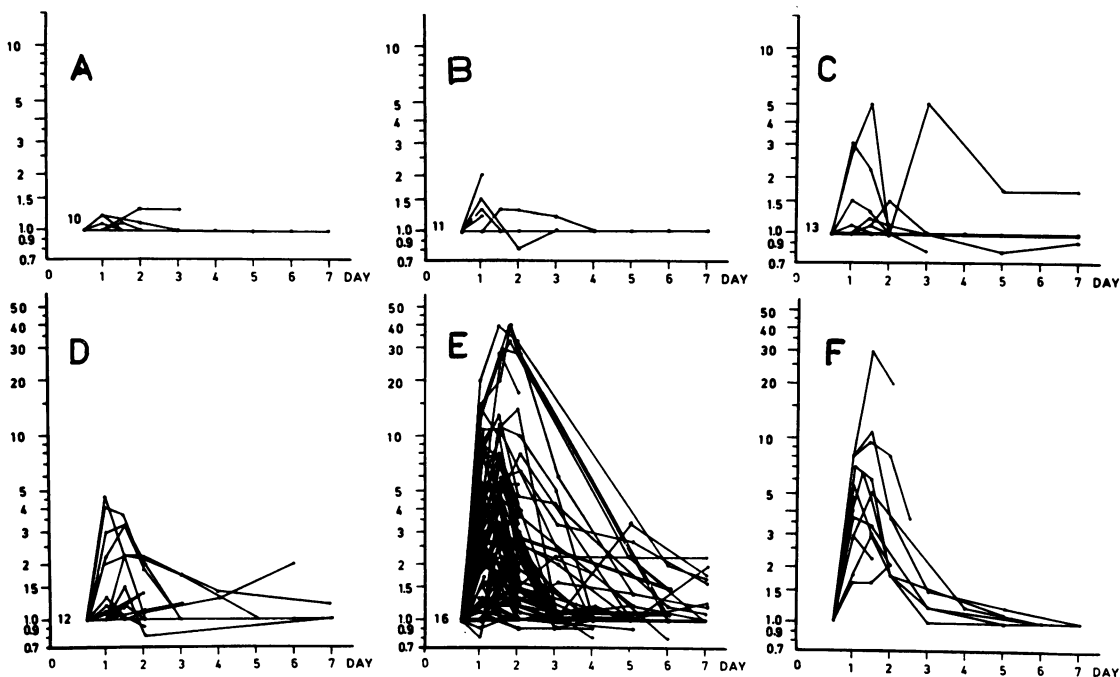
examination. Attempts were made to obtain blood samples six hours after the examination, and on the day following—that is, after 16-21 hours—and every second day for one week after examination. The total activity of serum amylase and the specific determination of salivary and pancreatic components of serum isoamylases after agarose gel electrophoresis in barbital buffer pH 8.8 were performed as described earlier (Skude, 1975a, b) using a dyed starch polymer (Phadebas Amylase Test, Pharmacia, Uppsala, Sweden) as substrate.

## Results

### INITIALLY NORMAL PANCREATIC AMYLASE

#### 1. Degree of contrast filling

Two hundred and three cases had normal serum activity of pancreatic isoamylases before the examination. Fifteen of these patients were subjected to single duodenoscopy with a mean rise in serum amylase activity to 1.06 times the original value, one of them rose 1.3 times (Fig. 1A); 16 patients in whom the ampulla of Vater was recognized and repeatedly picked upon with the tip of the catheter without



**Fig. 1** Increase of pancreatic isoamylase activity in serum after A: duodenoscopy, B: picking on the papilla of Vater, C: contrast filling of the bile duct system only, D: contrast filling of the main pancreatic duct, E: contrast filling of the main pancreatic duct and branches, and F: acinar contrast filling of the pancreas. The figures in the left lower corners indicate the number of individuals with unchanged activities throughout the observation period. In all cases the pancreatic serum amylase activity was normal before the examination.

successful cannulation had a mean increase in pancreatic serum amylase of 1.12, four of them increased 1.3 times or more the initial value (Fig. 1B). The bile duct system was cannulated and opacified in 21 individuals, of whom five—that is, 24%—had more than 1.3 times increased serum amylase levels, the mean increase became 1.38 times the original level (Fig. 1C).

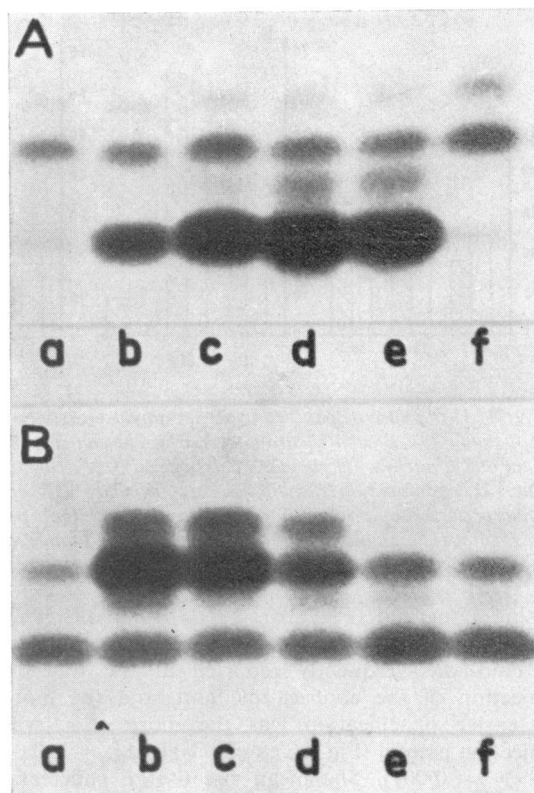
The pancreatic main duct only was opacified in 29 individuals. Nine—that is, 31%—of these had a rise in pancreatic serum amylase activity being more than 1.3 times. The mean increase was 1.70 times control (Fig. 1D). Among the 110 cases in whom the main pancreatic duct and its branches became opacified, 80% experienced an increase in pancreatic serum amylase level (Fig. 1E). The mean rise was 5.27 times over control. Acinar opacification of the pancreas was associated with increased levels of the pancreatic isoamylases in all 12 cases (Fig. 1F). The mean maximal increase in this group was 7.4 times over control levels.

Thus, in patients with normal serum levels of the pancreatic isoamylases before examination, there was a striking correlation between the type and extent of opacification and the rise of pancreatic serum amylase activity. Differences did not occur in the response of serum amylase activity whether the pancreatic duct system visualized included only the head (12 cases), the head and body (11 cases) or the whole gland (128 cases). After successful retrograde filling of the pancreatic duct system, a total of 60% of patients developed pathologically increased total serum amylase activities due to increase of the pancreatic isoamylases.

A large rise sometimes occurred in pancreatic isoamylase activity without much effect on the total amylase in serum (Fig. 2A). In 34 cases—that is, 23%—there was an increase of the level of pancreatic isoamylases in serum to more than 1.3 times of the initial value, although the total serum amylase activity still remained within the limits of values considered normal (up to 300 U/l). In one of these patients the rise was 6.0 times and in another 8.0 times over the control values. In the latter instance the total serum amylase activity rose only from 48 to 112 U/l.

The maximal increase of the pancreatic isoamylases usually occurred in the samples obtained six to 21 hours after examination. If the rise did not exceed 10 times the control level, it usually returned to control by the second or third day after examination. A rise of 40 times over control persisted at an abnormally high level for several days (Fig. 1).

Increases of the serum activity of pancreatic amylase which varied from 1.5 to 3.0 times control were recorded in some patients on the third to



**Fig. 2** A. Successive changes of serum isoamylase pattern after pancreatography showing 30-fold increase, from 15 to 450 U/l, of pancreatic isoamylase activity in serum. Total serum amylase activity increased from 120 to a maximum of 555 U/l. Sample (a) before examination, (b) immediately after, (c) six hours, (d) 12 hours, (e) 21 hours, and (f) five days after examination. B. Successive changes of serum isoamylase pattern after pancreatography showing 10-fold increase of salivary isoamylase activity. Sample (a) before examination, (b) immediately after, (c) six hours, (d) 20 hours, (e) three days, and (f) five days after examination. Maximum total serum amylase activity was 1230 U/l. Anode above.

seventh day after ERCP. These patients had either been subjected to bile way operation with cholangiography, been examined with coeliac angiography, or were chronic alcoholics who had been drinking.

## 2. Contrast medium and pain

Injection of Isopaque 350 was associated with a greater increase of the pancreatic serum amylase activity than was Urografin 60% (Fig. 3A), ( $\chi^2 = 7.5$ , d.f. = 2,  $0.025 > P > 0.01$ ). When Isopaque 350 was used, the branches were more often opacified and the frequency of acinar filling was higher than when

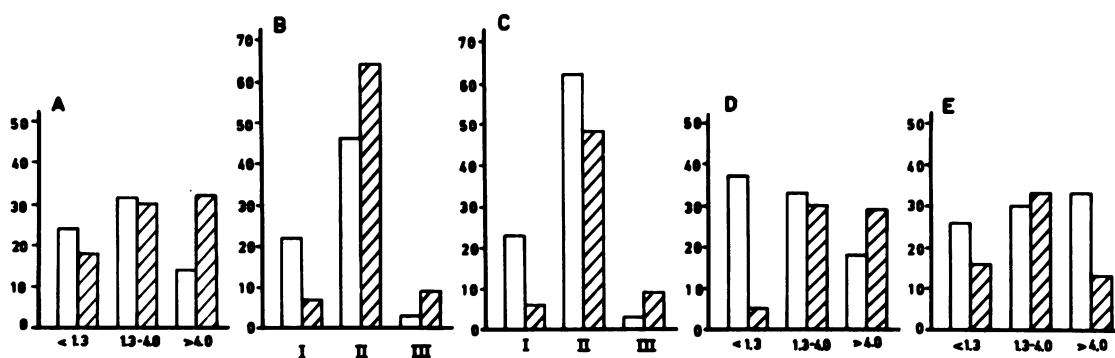


Fig. 3 A: increase of pancreatic serum amylase activity in relation to different contrast media (□ Urografin 60%, ▨ Isopaque 350). B: opacification with different contrast media. I: opacification of main duct. II: opacification of main duct and branches. III: acinar opacification (key as in A). C: pain in relation to opacification. I: opacification of main duct. II: opacification of main duct and branches. III: acinar opacification (□ absence of pain, ▨ pain). D: increase of pancreatic serum amylase in relation to pain (symbols as in C), and E: increase of pancreatic serum amylase activity in roentgenologically normal (□) and abnormal pancreatograms (▨).

using Urografin (Fig. 3B), ( $\chi^2 = 13.2$ , d.f. = 2,  $P \approx 0.001$ ).

Pain was frequently reported at the time of injection of the contrast medium, and the more extensive opacification was, the more often was injection painful (Fig. 3C), ( $\chi^2 = 10.8$ , d.f. = 2,  $0.01 > P > 0.001$ ). The mean rise of the pancreatic isoamylase activity in serum was higher in the patients who reported pain (Fig. 3D), ( $\chi^2 = 23.1$ , d.f. = 2,  $P < 0.001$ ). When Urografin 60% was used, 38% of patients reported pain, but, when Isopaque 350 was used, 45% reported pain; this difference was not significant statistically.

There was no correlation between the amounts of sedative and spasmolytic medications given in connection with the examination and the magnitude of the rise in amylase activity.

### 3. Pancreatic morphology

Patients in whom the pancreatograms were normal exhibited changes of original pancreatic amylase activity that was distributed about equally into three groups: less than 1.3—that is, no significant change—between 1.3 and 4.0, and more than 4.0 times the control level (Fig. 3E). Patients with abnormal pancreatograms more frequently exhibited rises between 1.3 and 4.0 times the initial values ( $\chi^2 = 6.9$ , d.f. = 2,  $0.05 > P > 0.025$ ). The abnormal pancreatograms included signs of pancreatitis—that is, obstruction, stenosis, dilatation, narrowing, beading, calculi, cysts, dislocation, and rigidity (Ariyama *et al.*, 1974) as well as pancreatic carcinoma. These two groups of diseases did not differ with respect to the occurrence of pancreatic hyperamylasaemia after ERCP. The

pancreatograms disclosed cysts in nine cases but these patients did not develop more extensive pancreatic hyperamylasaemia than did the others.

Fourteen examinations were performed in patients subjected to pancreatojejunostomy according to DuVal or Puestow-Gillesby. In six of the patients in whom the contrast material passed through the stoma, pancreatic serum amylases did not change. In the other eight cases, in whom the contrast material did not pass through the stoma, three developed significant pancreatic hyperamylasaemia.

### INITIALLY INCREASED PANCREATIC AMYLASE

In patients initially having pathologically elevated activities of pancreatic isoamylases in serum (above 175 U/l (Skude, 1975a) 31 examinations were performed (Fig. 4). In 23 cases the pancreatic duct was cannulated with opacification of the main duct and branches, and in three cases there was an acinar filling. Thus, the frequency with which acinar opacification occurred in this group did not significantly deviate from the frequency found in patients with initially normal pancreatic amylase activities. The maximal levels of pancreatic isoamylase activity were not higher than those observed among the patients with initially normal values.

### SALIVARY ISOAMYLASE

In 24 cases—that is, 12% of the examinations in persons initially having normal pancreatic isoamylase activity in serum—the activity of the salivary isoamylases in serum increased to a level more than 1.3 times the initial activity; the maximal increase was 10

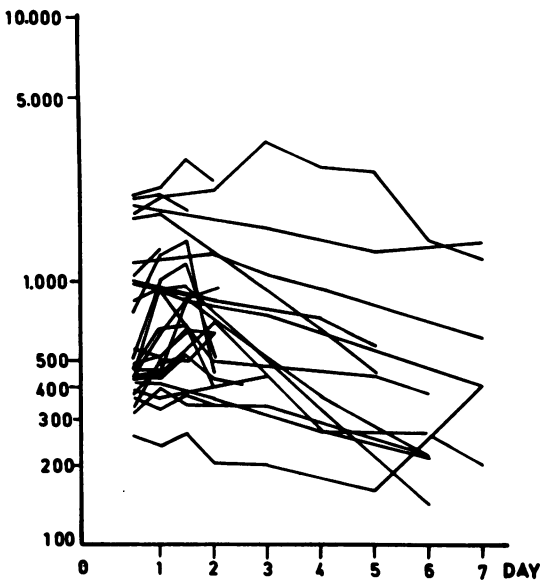


Fig. 4 Change of pancreatic isoamylase activity in serum of patients having increased activities before performing the examination.

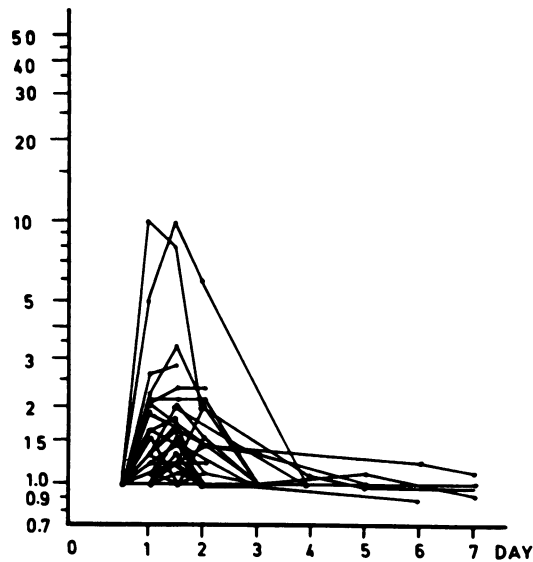


Fig. 5 Increase of salivary isoamylase activity in serum after duodenoscopy and pancreatography.

times (Figs. 2B and 5). Seven of them had a greatly increased salivation during the examination; their mean rise was 4.1 times. In 17 patients without increased salivation the mean rise was 1.9 times. In 14 of the examinations—that is, 7%—a pathologically increased total serum amylase activity was due to the salivary and not to the pancreatic isoamylases.

#### SEVERE COMPLICATIONS

Icterus began four days after ERCP and was prolonged in one patient who also developed bilateral peroneus paresis and diabetes mellitus. The symptoms, except the diabetes, regressed on steroid treatment. Two patients had attacks of acute pancreatitis—that is, persistent abdominal pain, increased activity of pancreatic serum amylase, elevated white cell count, and fever—the first week after the examination.

#### Discussion

The results of the present investigation show clearly that elevation of the pancreatic serum isoamylase activity after retrograde pancreatography correlates directly with the extent of opacification of the pancreatic duct system. The greatest elevations of total serum amylase activity and the highest frequencies of elevation occurred after complete filling of the acini as previously reported in other studies (Kasugai *et al.*,

1971; Cotton, 1972; Kasugai *et al.*, 1972). Single cholangiography or even attempts at cannulation resulted, however, in pancreatic hyperamylasaemia in about 25% of cases. This is the same frequency of elevation that occurred when the main pancreatic duct was visualized without filling the acini or branches. It is conceivable that these simple manipulations provoke spasm or oedema of the papilla. Increases in intraductal pressure may result in leakage of the pancreatic secretions into the circulation. In concert with this proposal was the finding that serum amylase did not rise in patients with open pancreatojejunostomies. The greater prevalence and higher levels of elevation seen after filling of the small ductal branches and parenchyma may result from rupture of the acini. A high injection pressure and a large volume of injection into the pancreatic duct is known to cause higher and more prolonged hyperamylasaemia in dogs (Waldron, 1968).

The chemical composition of the contrast medium had effects on the degree of opacification as well as on the discomfort associated with the injection of the contrast material and on the hyperamylasaemia. Reasons for this are possibly related to differences in the contrast material itself, viscosity, osmolarity, or local toxic effects of the substances injected. Thus, Isopaque 350 which was more often associated with untoward effects has higher iodine content and osmolarity but lower viscosity than Urografin 60%.

Just why the frequency of marked elevations of the pancreatic serum amylase levels was greater in patients with normal pancreatograms in contrast with those with abnormal pancreatograms is obscure. Cotton (1972) made a similar observation.

Takeuchi and associates (1974) reported separation of individual serum isoamylases after endoscopic pancreatography. They found no case of increased salivary serum isoamylases after cannulation in an unstated number of subjects. Cannulation caused an abnormally high total serum amylase activity due to elevation of salivary isoamylase in 7% of our examinations. The reason for the elevated salivary isoamylase in the circulation is not entirely clear but may result from increased salivation due to the irritation of the fiberoendoscope. It is also possible that a temporary obstruction of the ducts of the sublingual salivary glands occurs in some manner (Slaughter and Boyce, 1969).

The frequency and degree of hyperamylasaemia were not in any way different in patients who had elevated pancreatic serum amylase levels before the endoscopic examination as compared with those with normal pre-examination values. Thus, elevated values of serum amylase cannot be used as a contraindication to the examination. This is in accord with the findings of Blackwood *et al.* (1973) who reported that patients with elevated urinary amylase activities during four weeks preceding examination did not have an increased frequency of post-cannulation pancreatitis.

Thus, at present, there is a small but significant risk of ERCP, which stresses the need for further research directed towards reducing the frequency of complications. Besides, at present, nothing is known about the potential long-term effect of the insult caused by ERCP. High injection pressure and overfilling of duct system are thought to be the main reasons for pancreatic complications. The present study

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also indicates a relationship between complications and the contrast medium. Furthermore, it clearly shows the need for partition of the isoamylases to interpret the data properly.

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