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Experimental acute pancreatitis in the rat—a new model

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SUMMARY A new experimental model of acute pancreatitis in the rat has been devised. It consists of a closed duodenal loop into which infected bile is injected under pressure; intestinal continuity is maintained by a plastic tube passed through the loop. Histological and biochemical evidence of acute pancreatitis in the rat model is presented. The model has been compared with that of Nevalainen and with control groups of rats undergoing bile duct ligation and sham operation. The model produces a consistently fatal acute pancreatitis, more severe than that produced by Nevalainen's model, with a survival time of $28 \pm 12{\cdot}8$ (SD) hours. A combination of the reflux of infected bile under increased pressure into the pancreatic duct, at a known time, produces a model which may be suitable for the investigation of therapeutic agents.

Experimental acute pancreatitis in animals can be produced either by creating a closed duodenal loop[1, 2] or by injecting various substances into the pancreatic ducts under pressure.[3] Cannulation of the pancreatic duct in the rat is difficult and injection into the pancreatic substance may not be accurately reproducible. We have found the pancreatitis produced by closed loop alone to be inconsistent in its development and variable in its severity. A model has been devised which incorporates a closed duodenal loop into which infected bile is injected under pressure.

Method

Four groups (1-4) of Sprague Dawley rats weighing between 250 g and 300 g were studied. The animals received no nourishment other than water *ad libitum* for a period of 24 hours preoperatively. A laparotomy was performed under ether anaesthesia. In group 1, comprising the experimental pancreatitis group under investigation, a gastrotomy was made and a plastic tube (10 French Gauge) 4 cm in length was manoeuvred into the duodenum; a closed duodenal loop was created by ligating the duodenum around the plastic tube (Fig. 1). The proximal ligature was placed immediately distal to the pylorus and the distal one well beyond the entry of the pancreatic duct. Before ligating the proximal ligature,

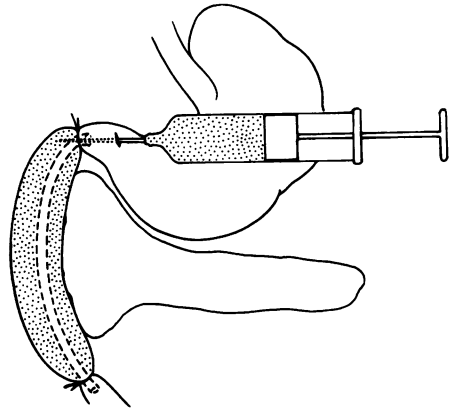

Fig. 1 *Rat model: acute pancreatitis. Diagrammatic representation of experimental method. A closed duodenal loop with an indwelling plastic tube is illustrated. Human bile (stippled area) is injected under pressure into the closed loop.*

infected human T-tube bile was injected into the closed loop around the plastic tube until the duodenum was distended (Fig 1). The organisms present in the injected T-tube bile were *Escherichia coli* and *proteus*. The duodenal blood supply was carefully preserved. Bile could be seen to dilate the pancreatic ducts at the time of injection. On recovery from anaesthesia, 3 mg per kg body weight of pethidine was given intramuscularly eight hourly. Free access to food and drink was allowed and the condition of the animals was carefully observed at regular intervals. Blood samples were taken at

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20 hours postoperatively and assayed for amylase by the Phadebas method. The animals were kept until death or those surviving five days were then killed. Immediately after death the pancreas was removed and examined histologically.

Eighty-five rats were used in the study. In 50 the model was created as described and these were compared with three control groups: group 2, laparotomy and bile duct ligation—10 rats; group 3, laparotomy and gastrotomy with and without the installation of bile into the duodenum—15 rats; group 4, closed duodenal loop with an intraduodenal tube but without bile (Nevalainen's model)—10 rats.

Results

The results were assessed in terms of the macroscopic appearance, histological changes, plasma amylase levels, and survival time.

MACROSCOPIC APPEARANCE

Rats in groups 1, 2, and 4 became jaundiced. Groups 1 and 4 showed evidence of pancreatic oedema and haemorrhage with occasional surrounding fat necrosis and blood stained fluid in the peritoneum. Gastric dilatation was occasionally present, although vomiting did not occur and free fluid was present

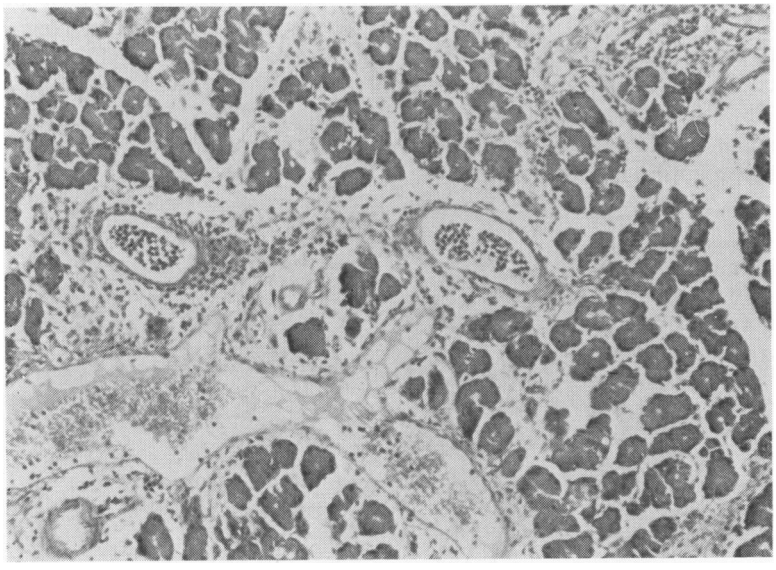

Fig. 2 *Photomicrograph of rat pancreas 20 hours after the induction of acute pancreatitis using the new model. It shows interstitial oedema and diffuse infiltration by numerous acute inflammatory cells.*

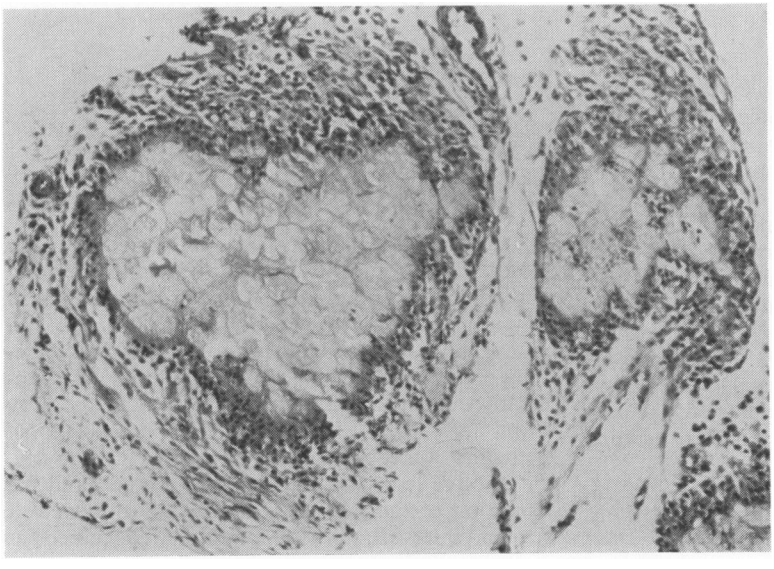

Fig. 3 *Photomicrograph of peripancreatic fat from a rat 20 hours after the induction of acute pancreatitis. It shows fat necrosis surrounded by an acute inflammatory cell response.*

in the pleural cavities of 20% of the test animals. Portmortem findings on the rats with ligated bile duct and those with gastrotomy alone showed no evidence of pancreatic disease.

HISTOLOGICAL FINDINGS

The histological changes found in the pancreas of group 1 varied from oedema to large abscesses in relation to the ducts. Surface inflammatory change was invariably present and occasional foci of fat necrosis were noted. Most cases had interstitial oedema and diffuse infiltration by varying numbers of polymorphonuclear leucocytes (Figs. 2 and 3). Similar changes were seen in the pancreas in group 4. No evidence of pancreatic disease was seen in the other control groups (2 and 3).

Table 1 *Plasma amylase values ±1 SD in test rats and four control groups*

		Plasma amylase	
Groups	*No.*	*No. over 10000 units*	*Mean*
Normal	10	0	7100±1474
Closed loop+bile	10	8	16775±7390
Closed loop	10	7	15565±10659
Gastrotomy	10	2	6364±3301
Bile duct ligation	5	1	7613±5496

AMYLASE VALUES

The serum amylase concentration is shown in Table 1. Estimations were first performed on blood obtained from 10 normal rats which had no procedure performed. The mean amylase level was 7100±1474 SD units, a level in excess of 10000 units was regarded as abnormal in this study. The test animals and the closed loop controls had markedly raised plasma amylase levels in comparison with the controls.

Table 2 *Number of rats in each experimental group and number that died within five days in each of these groups*

	Survival time		
Experimental group	*No.*	*Dead*	*Mean±ISD (h)*
Closed loop+bile	50	50	28±12·8
Closed loop	10	8	55±42
Bile duct ligation	10	0	
Gastrotomy	10	0	
Gastrotomy+bile in duodenum	5	0	

The mean survival time ±1 SD is given for the 50 test rats (closed loop+bile) and the 10 rats with acute pancreatitis induced by a closed loop without the addition of bile. The difference is significant ($P<0.05$).

SURVIVAL TIME

In Table 2 the survival data for each group is shown. All the test rats died. The mean survival time was 28±12·8 SD hours. Two of the 10 closed loop rats without bile were still alive and well after five days. The mean survival time was 55·3±42 SD hours. None of the rats in the other two control groups died during the course of the experiments.

Discussion

The rat is an economical and convenient laboratory animal. Lankisch[4] and Hansson[5] both reported models of acute pancreatitis in the rat which required cannulation of the pancreatic duct and the injection of bile, bile salts, or other toxic substances. Nevalainen (1975)[1] described a model in the rat in which acute pancreatitis was induced by creating a closed duodenal loop; by using a transluminal duodenal tube, intestinal obstruction was overcome. We believe that the model described here is an improvement on that of Nevalainen, as it produces a more consistently severe acute pancreatitis in the rat with an accurately determined time of onset and a more predictable survival time than we have recorded with Nevalainen's model. The model combines increased intrapancreatic duct pressure, bile reflux, and infection in the development of a severe and fatal form of pancreatitis.

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