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Alterations in Tissue Reactivity of Thoracic Duct Lymph Produced by Retention of Excess Pancreatic Secretion.* (30680)

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Fluid containing physiologically active substances of pancreatic origin flows from the normal pancreas *via* lymphatics to the cisterna chyli and thoracic duct and thence to the subclavian vein. This accessory outflow tract for pancreatic secretion serves both as a safety cistern siphoning off excess acinar fluid from the interstitium and duct system and as a constant source of normally circulating pancreatic enzymes(1). An intimate anatomical relationship between intrapancreatic lymphatics and the exocrine system was described by Hoggan in 1881 and recently by Duprez in 1964 which is in keeping with this view(2,3).

The effects on the pancreas of impairment to flow of either thoracic duct lymph or pancreatic juice are compounded when one condition is superimposed on the other. Chronic lymphatic obstruction at the cisterna chyli causes massive lymphedema of the pancreas as does ligation of the thoracic duct in the neck(4). On the other hand, it is well known that obstruction of the pancreatic duct system is followed by ductal distension with gradual atrophy of acinar tissue; although foci of inflammation and necrosis do appear, Opie was the first to demonstrate that these lesions are barely noticeable microscopically and take weeks to develop(5). When lymphatic and ductal obstruction are combined massive necrosis develops within 24 hours(6).

Certain characteristics of the distribution of fat necrosis in the pleural and peritoneal cavities in patients with acute pancreatitis led to experiments by Perry which provided evidence for lymphatic dissemination of pancreatic lipase(7). Although lymphatic dissemination of lipase probably explains distribution of these lesions, it is generally conceded that pancreatic enzymes alone are incapable of injuring intact living tissue. This report pre-

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sents evidence which indicates that as the pancreas distends with undrained acinar secretion and interstitial fluid increasing amounts of pancreatic enzymes as well as substances capable of initiating acute inflammation appear in thoracic duct lymph.

Methods. Twenty healthy adult mongrel dogs were anesthetized with intravenous sodium pentobarbital 1 mg/kg and operated upon through a right thoracotomy incision. The thoracic duct was exposed in the lower right thorax, cannulated with polyethylene tubing, and control samples of thoracic duct lymph were collected. Following intravenous administration of secretin (160 clinical units Boots) and bethanechol chloride (5 mg), additional lymph samples were collected at hourly intervals for 3 hours. Lymph flow rates were measured and amylase determined by Agren and Lagerlof's method(8). An aliquot of 0.15 ml from each lymph sample was injected into the subcutaneous tissues of adult rats and the animals were sacrificed 48 hours later. The injection sites were excised, fixed in buffered formalin, sectioned and stained with hematoxylin and eosin.

The dogs were divided into 5 equal groups and prior to administration of secretin and bethanechol chloride the experimental procedure was varied as follows (Fig. 1).

Group I Lymph was allowed to drain freely during the entire length of the experiment.

Group II as in Group I but both pancreatic ducts were obstructed by transduodenal suture ligation.

Group III Thoracic duct lymph flow was obstructed by clamping the cannula. At the end of every hour the cannula was unclamped and sample collected.

Group IV as in Group III together with pancreatic duct ligation.

Group V as in Group IV except that the common bile duct was cannulated and bile allowed to drain freely.

Results. One or more of the hourly lymph samples collected from each of the 20 dogs following administration of secretin and bethanechol chloride produced an acute inflammatory reaction when injected into the subcutaneous tissues of rats. Accumulation of exuded polymorphonuclear cells and lymphocytes, erythrocytes and extensive interstitial edema characterized these lesions (Fig. 2 A, B). Extent of the inflammatory reaction varied within certain limits. The most marked exudative lesions developed following injection of lymph samples obtained from dogs undergoing both pancreatic duct and intermittent lymphatic obstruction. Less severe reactions developed after injection of lymph from dogs undergoing either of these procedures alone. Injection of lymph from dogs undergoing neither procedure but actively secreting pancreatic juice was followed by an inflammatory reaction which was less marked than that seen in the other experiments. Control samples of lymph obtained from each dog prior to injection of secretin and bethanechol chloride were without effect. Amylase content of the lymph rose rapidly in all dogs after injection of secretin and bethanechol chloride (Table I).

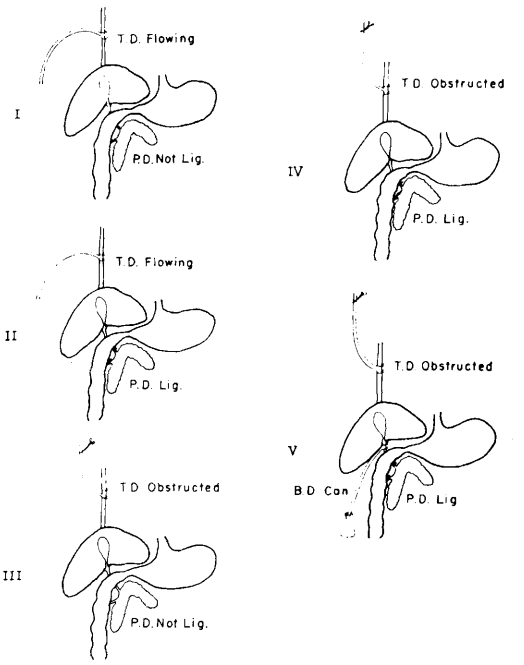

FIG. 1. Diagram of experimental procedures carried out in 5 groups of dogs (P.D. Pancreatic Ducts; T.D. Thoracic Duct; B.D. Bile Duct).

In all dogs subjected to pancreatic duct ligation the lymph became icteric due to the fact that the common bile duct was included in the ligature(9). To avoid any effects that biliary components might have on substances

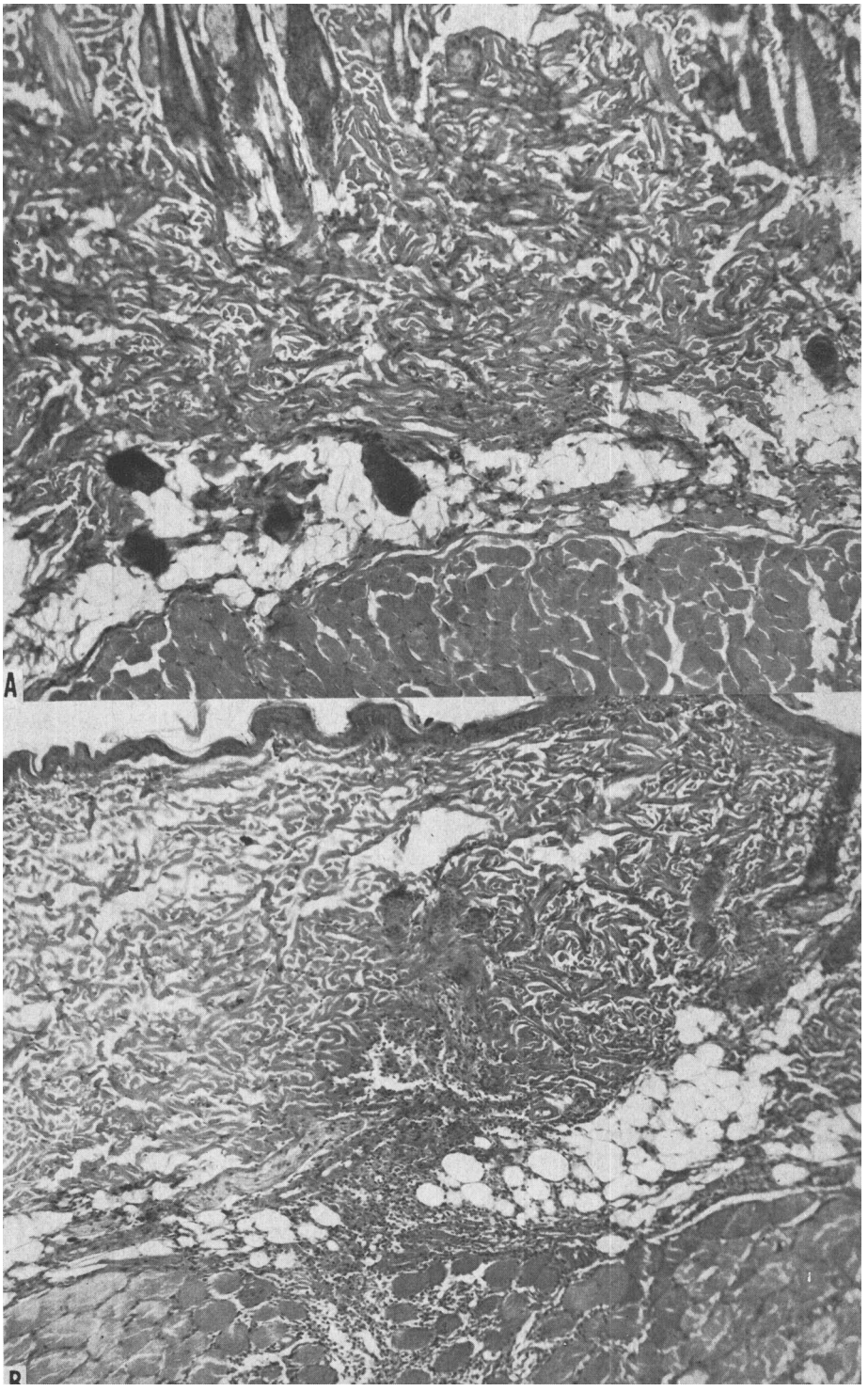

FIG. 2 A & B. Sections of skin and subcutaneous tissue removed from a rat 48 hr after subcutaneous injections of thoracic duct lymph. The sample of lymph injected at A was obtained before, and at B, after intravenous administration of secretin and bethanechol chloride to a dog with thoracic duct obstruction. (× 50.)

TABLE I. Concentration of Amylase in Thoracic Duct Lymph Before and After Intravenous Administration of Secretin and Bethanechol Chloride.

	Dog No.	Amylase (mg glucose/100 cc) concentrations in lymph			
		Control lymph	Lymph 1	Lymph 2	Lymph 3
Group I	90	1,080	49,200	126,000	106,200
P.D. not ligated	93	1,020	19,600	23,000	34,200
T.D. flowing	104	600	11,700	8,400	4,000
	105	880	11,100	26,400	8,000
Group II	68	720	19,980	12,960	15,360
P.D. ligated	69	1,320	63,800	67,800	41,400
T.D. flowing	83	900	1,290	33,600	32,500
	85	1,020	42,600	53,600	40,500
Group III	61	1,080	—	21,200	—
P.D. not ligated	71	720	21,000	48,800	—
T.D. obstructed	76	900	39,300	18,400	13,800
	80	1,320	19,800	66,800	71,500
Group IV	73	1,120	7,800	10,800	26,500
P.D. ligated	77	1,320	15,900	30,000	40,000
T.D. obstructed	78	720	19,800	22,800	25,500
	81	900	25,800	48,400	53,500
Group V	66	900	2,240	—	—
P.D. ligated	72	1,600	14,400	18,000	20,500
T.D. obstructed	74	480	15,000	32,400	27,000
Bile duct cannulated	75	900	39,300	18,400	13,800

in thoracic duct lymph, the common bile duct was drained in 4 dogs during the entire period of pancreatic duct and lymphatic obstruction. Although lymph did not become icteric in these dogs it produced an inflammatory reaction of the same magnitude as that seen when lymph from similarly prepared animals without bile diversion was used.

The pancreas became grossly edematous and congested in dogs subjected to both lymphatic and pancreatic ductal obstruction. These changes were not observed in dogs subjected to pancreatic duct ligation alone.

Discussion. Simultaneous injection of secretin and bethanechol chloride results in rapid formation of a large volume of alkaline pancreatic secretion containing high enzyme concentrations(9). When the pancreatic exocrine system is suddenly distended by such excess pancreatic secretion unidentified substances appear in thoracic duct lymph which have the property of inducing acute inflammation. At the same time lymphatic transport of amylase and probably other enzymes from the pancreas increases.

Experiments by Wells in 1903 indicated that pancreatic extracts in which all enzyme activity had been destroyed by heat still retained the capacity to initiate inflammation (10). Later Dragstedt showed that intact living tissue was unaffected by enzymes in pancreatic juice(11). In a large number of articles published recently which deal with pancreatitis these important observations of Wells and Dragstedt are completely overlooked. In the experiments reported here the fact that the severity of the inflammatory reaction increased with lymphatic and/or exocrine duct obstruction, maneuvers which did not influence peak levels of enzymes in lymph, similarly suggests that levels of pancreatic enzymes alone were not the important factors in producing the inflammation. Release of substances which initiate inflammation seemed to depend solely upon factors which regulate pancreatic interstitial pressure.

Retrograde injection of concentrated bile from the gall bladder into the pancreatic duct is a common experimental method for producing inflammatory edema of the gland. Although intraduodenal ligation of the pancreatic ducts excluded any possibility of bile entering the pancreas, this maneuver did obstruct the common bile duct and as expected thoracic duct lymph became icteric(12). Nonicteric lymph, however, obtained from dogs subjected to exocrine duct and lymphatic obstruction and draining bile through a cannula

initiated inflammation as did lymph from dogs undergoing thoracic duct obstruction alone, pancreatic duct obstruction alone or neither one of these procedures. Whether or not components of bile reached thoracic duct lymph was therefore not critical.

Role of the lymphatic system in the pathogenesis of pancreatic inflammatory disease in man is obscure. Recent experimental data indicate that flow capacity in the thoracic duct in man is limited and that lymph does not flow continuously through the lymphatic venous junction in the neck(13). Further, data acquired from experiments still in progress indicate that when the pancreatic exocrine system is obstructed thoracic duct lymph flow is an important mechanism regulating intraductal pressure. It seems reasonable to speculate that in patients actively secreting acinar fluid against exocrine flow resistance the normal impairment of thoracic duct lymph flow at the lymphatic venous junction may be a critical factor in the control of pancreatic interstitial pressure and release of substances capable of initiating inflammation.

Summary. Sudden distension of the pancreatic exocrine system by excess pancreatic secretion releases substances into thoracic duct lymph which initiate an acute inflammatory reaction when injected into rats. Lymph becomes more potent in this respect when either the exocrine duct system or the thoracic duct is obstructed and especially when these two maneuvers are combined.

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Effects of Hypophysectomy on Lipolytic Response of Adipose Tissue To Pituitary Hormones.* (30681)

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An intact pituitary gland appears to be required for normal responsiveness of adipose tissue to hormones. Hypophysectomy increases the sensitivity of adipose tissue to the insulin-like actions of growth hormone(1). Similarly, pituitary ablation decreases the effects of epinephrine on free fatty acid (FFA) mobilization(2,3,4). The present report describes the effects of hypophysectomy on the sensitivity of adipose tissue to the lipolytic actions of corticotropin (ACTH) and thyrotropin (TSH).

Materials and methods. Male rats weighing 100-120 g were obtained from the Charles River Breeding Laboratories and were maintained on Purina Lab Chow. Hypophysectomized rats were studied 2-4 weeks postopera-

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