Lymphatic Pathway of Pancreatic Secretion in Man *

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PHYSIOLOGICALLY-ACTIVE products of pancreatic metabolism are assumed to leave the pancreas either through the ductal system into the duodenum or directly into venous capillaries. The intimate anatomical arrangement of acinar tissue and ductules on one hand and islet tissue and capillaries on the other is in keeping with this view of pancreatic function.

Based on this concept, many experimental investigations of inflammatory disorders of the pancreas and efforts at treatment have been directed toward alteration of patterns of flow and pressure in the exocrine ductal system. Diversion of flow by anastomoses, decompressive operations and reduction of resistance to flow by sphincterotomy are examples of this application.

In this report evidence suggesting an additional outlet for pancreatic products will be considered. This evidence, acquired through studies of flow and composition of thoracic duct lymph in human patients with and without pancreatic disease, indicates that fluid, containing physiologically active substances of pancreatic origin, flows from the pancreas via lymphatics to the cisterna chyli and thoracic duct.

Transport of pancreatic interstitial fluid directly into the thoracic duct has been explored before, notably by Bainbridge,[2] in 1902. He demonstrated, while working in Starling's laboratory, that in fasting dogs the rate of flow of thoracic duct lymph increased after secretin administration. In 1937, Blalock [3] showed in dogs that lymphatic obstruction at the cisterna chyli caused massive lymphedema of the pancreas. Surgeons recognize that following splenectomy, peritoneal fluid, rich in pancreatic enzymes, accumulates in the area and is related to transection of pancreatic lymphatics at the hilus of the spleen.

Extravasation of fluid containing enzymes from an inflamed pancreas into the peritoneal cavity, with subsequent absorption by peritoneal lymphatics, is a separate although related situation. This indirect route of entry to the blood through lymph channels has been studied by many investigators including Opie,[16] Wells,[22] Perry [17] and Egdahl.[10]

Methods

The thoracic duct was cannulated in the neck in 26 patients by the method of Linder and Bloomstrand.[15] Ten patients had no known abnormalities of pancreatic function. Six patients were known to have or have had pancreatic inflammatory disease. Ten other patients will not be considered in this paper because the observations made were directed toward factors other than the pancreas which might influence flow and composition of lymph.[5]

During most lymph collection periods the patients were conscious and at rest. On three occasions lymph was collected during

* Presented before the American Surgical Association, White Sulphur Springs, West Virginia, April 4, 1960.

Supported by U. S. P. H. S. Pancreatic Study No. 2-A-2785-(C1) and New York City, Department of Health, Health Research Council.

The technical assistance of Miss Amalia Martelli and Miss Thelma Cancro is gratefully appreciated.

TABLE 1. *Comparison of Lipase Concentrations in Lymph and Serum and Rates of Lymph Flow, before and after Intravenous Secretin Administration*

Lymph Flow (ml./min.) and Lipase Concentration (mg./100 ml.) in Response to Secretin

	Flow		Lymph		Serum	
Patient	Control	Secretin	Control	Secretin	Control	Secretin
M.C.	13	16.5	2.4	6.4	.6	1
J.T.	11	15	.7	1.9	1.6	1.8
P.A.	5	8	3.8	332	4	3
F.W.	11	14	.3	4	2.6	3
E.R.	7.8	6.9	.8	250	.6	.86

an abdominal operation. For at least 30 minutes before and after administration of 100 units of secretin, consecutive timed 10-minute lymph samples were collected and the volumes were recorded. Experimental conditions were varied on occasion in the following manner: 1) by obstructing pancreatic outflow into the duodenum through the administration of 10 mg. of morphine sulphate which contracted smooth muscle in the sphincter of Oddi and around the duct in the duodenal wall; 2) by manipulation of the pancreas at operation; and 3) by maintaining one patient on a diet consisting only of fat for two days prior to the administration of secretin. Lymph was analyzed for amylase, lipase, or both, and in some instances for pancreatic desoxyribonuclease. In most instances, the patient's circulating blood serum was similarly and concomitantly analyzed.

Amylase was determined by Lagerlof's method.[1] Pancreatic lipase activity was measured by Seligman's method,[19] as modified by Fishman,[11] using beta-naphthyllaurate as substrate. Desoxyribonuclease activity was determined by the methyl green reaction.[14]

Secretin used is a purified preparation produced and supplied by Eli Lilly Co.

Results

Administration of secretin alone or in combination with morphine to nine patients without pancreatic disease regularly resulted in an increase in enzyme concentration in thoracic duct lymph (Tables 1, 2). Descriptions of this response have appeared in preliminary reports.[6, 7] Increase in lymph enzyme concentration after secretin was accompanied by a transient increase in rate of flow of thoracic duct lymph, which was

TABLE 2. *Comparison of Amylase Concentrations in Lymph and Serum and Rates of Lymph Flow, before and after Secretin and Secretin and Morphine Administration*

Lymph Flow (ml./min.) and Amylase Concentration (units/100 ml.) in Response to Secretin + Morphine

	Flow			Lymph			Serum		
Patient	Control	Secretin	Secretin + Morphine	Control	Secretin	Secretin + Morphine	Control	Secretin	Secretin + Morphine
R.M.	5.2	5.5		325	755		525	475	
P.A.	6	8	8	320	1,980	2,850	310	345	400
M.R.	8		14.4	320		1,550	110		150
A.J.	5.3	8.2		270	805				
F.W.	11	14	14	120	530	650			
D.C.	4.2		5.3	170		2,000			
T.C.	13.5	12.5	12	310	710	1,875			

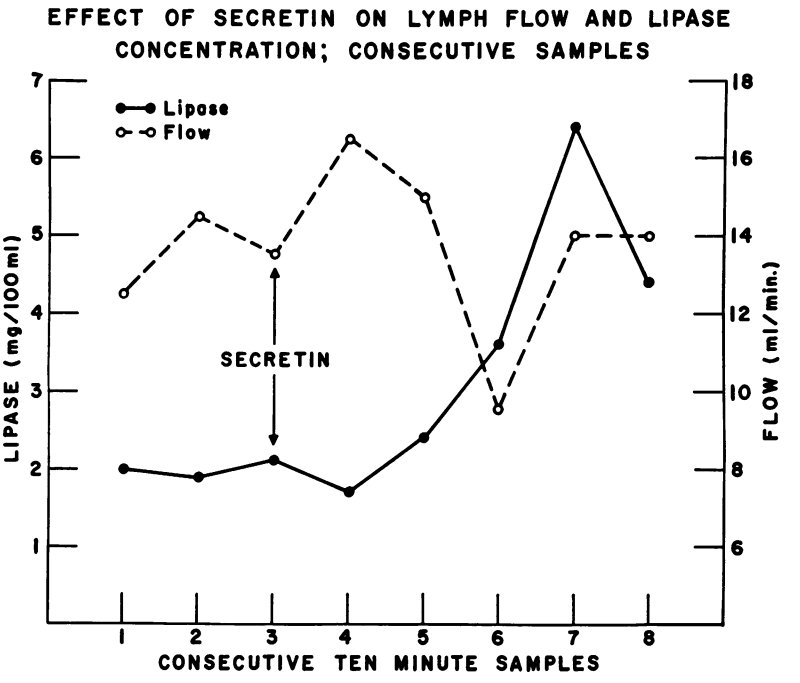

FIG. 1. Sequence of changes in rate of lymph flow and lipase concentration after secretin administration.

more marked in fasting patients. After the first ten or 20 minutes following secretin administration, however, rate of flow returned to normal and enzyme concentration continued to rise (Fig. 1). When morphine was combined with secretin, enzyme concentration was higher than with secretin alone (Fig. 2). Morphine alone had no ef-

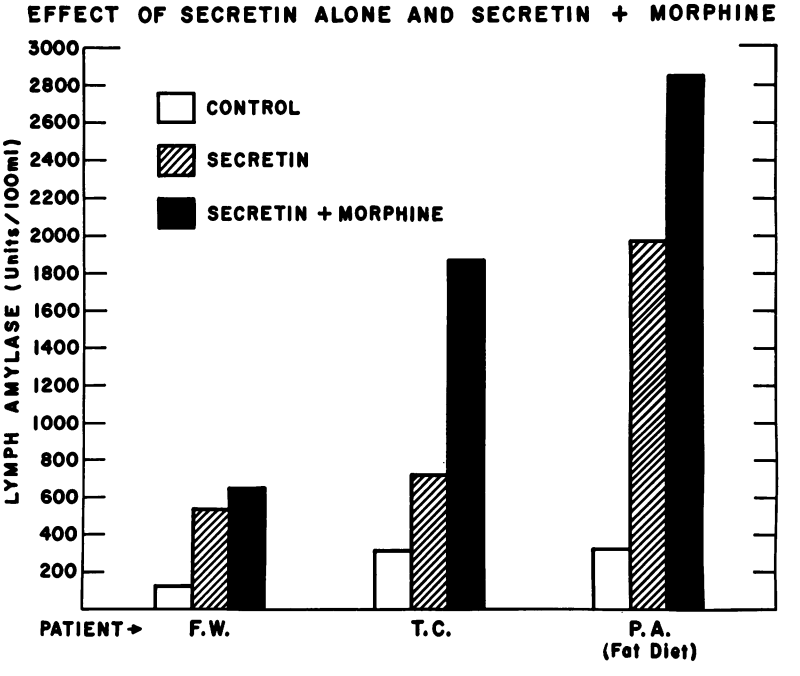

FIG. 2. Comparison of effect of secretion alone and secretin combined with morphine on lymph amylase concentration.

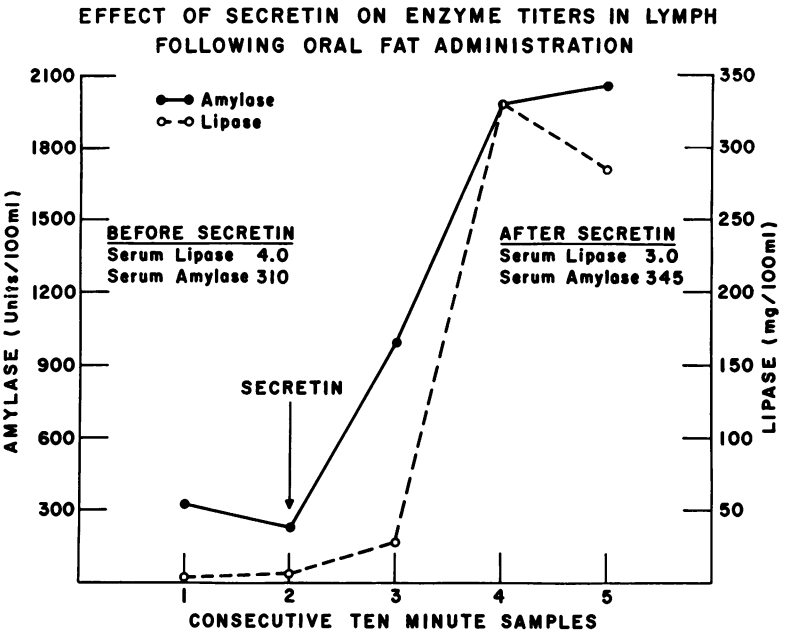

FIG. 3. Sequence of changes in lymph amylase and lipase concentrations after secretin administration, in a patient whose diet was limited to fat for two days prior to the experiment.

fect on enzyme concentration. The titer of enzymes in serum did not change significantly in any patient.

Desoxyribonuclease is normally present in thoracic duct lymph in about the same concentration as serum and in this respect is similar to amylase and lipase. The concentration rose in lymph, however, only when secretin administration was combined with morphine and not after secretin alone.

A striking increase in enzyme output in lymph was observed in the patient whose diet was limited to 100 Gm. each of corn oil and coconut oil on each of two days prior to secretin administration (Fig. 3). This patient died several weeks subsequent to these experiments, of cancer of the lung, and at autopsy the pancreas, gastro-intestinal tract and abdominal lymphatic system were found normal.

In an additional patient without pancreatic disease, thoracic duct lymph was collected during resection of the splenic flexure of the colon. Immediately following gentle handling of the pancreas, necessitated by the colon dissection, amylase and lipase titers in the lymph increased thirty-fold over that expected in the normal, and no further rise followed secretin administration. Serum levels remained normal.

Observations in six patients with pancreatitis (Table 3) may be outlined as follows: 1) secretin alone and secretin with morphine were given to a patient (L.B.) with diffuse pancreatic calcification and in whom both sphincterotomy and split pancreatico-jejunostomy (Roux-en-Y) had been performed previously. There was no change in flow or enzyme content of thoracic duct lymph; 2) flow and enzyme content of lymph were unchanged in a patient (S.K.) with fibrosed pancreas in whom a pancreatic pseudocyst was being drained externally; 3) administration of secretin alone to a patient (A.S.) known to have had one hospital admission for acute pancreatitis three years earlier, and who was treated by sphincterotomy, resulted in an increase in enzyme output in lymph; subsequently, when morphine was combined with secretin, no further rise occurred; 4) study of thoracic duct lymph in a patient (J.E.) 10 days after an episode of acute pancreatitis revealed elevated enzyme titers in both

lymph and serum; no secretin was administered; and 5) in two patients (M.S., W.H.) with chronic pancreatitis, manipulation of the pancreas at operation in one, and a pancreatogram in the other, resulted in an immediate rise in enzyme titer in the lymph, serum levels remaining unchanged.

Discussion

This investigation demonstrates that interstitial fluid formed in the pancreas is normally conveyed directly to the thoracic duct in lymph from the pancreas. In much the same way as Starling [20] pictured the lymphatics of the liver serving as a "safety cistern," enabling the liver to siphon off pressure increases in the hepatic veins and inferior vena cava, the lymphatics of the pancreas may be considered a "safety cistern" siphoning off pressure increases in the interstitium and duct system. Pancreatic lymphatics, in this manner, function to increase the capacity of the duct system for fluid, and expand the gland outlet as needed. Obstruction of pancreatic lymphatics outside the gland does not occur with any known clinical disease conditions. Even in animals, experimental production of such an obstruction is difficult,[3] due probably to extensive collaterals and ability of lymphatics to regenerate rapidly. On the other hand, recurrent acute pancreatic inflammation with tissue destruction, is followed by fibrosis. Even minimal fibrosis in the pancreas, however, may interfere with efficient lymph flow and prevent the lymphatics from acting as a safety valve, thereby reducing the expansibility of the whole gland. The fibrosed gland secretes against varying degrees of fine duct obstruction, intraductal pressure rises quickly, the pancreas becomes edematous and there is early extravasation of pancreatic juice into the peritoneal cavity. The data suggest, in the two patients with chronic pancreatitis and no secretin response, that interstitial fibrosis had developed to a degree which obstructed the lymphatic route of secretion. If, as is suggested in the fat fed patient, copious secretion accompanies fat absorption, this feature might help explain the fatty intolerance so characteristic of pancreatitis. In the patient in whom a sphincterotomy had been performed following recovery from one episode of acute pancreatitis, rise in enzyme titer after secretin administration indicates that the lymphatic pathway was still available, but because the sphincter was incompetent, morphine had no effect beyond that of secretin alone. Maneuvers less physiologic than secretin stimulation, such as manipulation of the gland and pancreatography change cell and capillary permeability and cause the same general enzyme increases in lymph whether or not fibrosis has occurred in the pancreas.

TABLE 3. *Amylase and Lipase Concentrations in Lymph and Serum and Rate of Lymph Flow in Patients Known to Have or Have Had Pancreatitis. For the First Three Patients the Effect of Secretin, and for the last Two, the Effect of Pancreatic Manipulation is Shown*

Patients with Pancreatitis: Changes in Enzyme Concentration and Lymph Flow

	Lymph Flow (ml./min.)		Lipase (mg./100 ml.)				Amylase (units/100 ml.)			
			Lymph		Serum		Lymph		Serum	
	Cont.	Exp.	Cont.	Exp.	Cont.	Exp.	Cont.	Exp.	Cont.	Exp.
L.B.	12.0	11.3	1.2	1.3	1.7	1.5	55	85	45	110
S.K.	8.0	9.3	1.7	1.7	3.0	2.0	170	170	430	85
A.S.	4.8	4.7					290	880	590	215
J.E.	10.0		2.1		1.8		1,045		840	
M.S.	3.0	6.3	0.7	6.0			45	260		
W.H.	7.5	15.0	2.0	186.0	4.6	5.1	430	1,120		

Flock and Bollman [12] have described the effect of food in general and fat diet in particular, on amylase content of lymph in the intestinal lymph duct of rats. This duct is believed to contain lymph from the pancreas. Their interpretation was that amylase is not secreted in increased amounts into pancreatic lymph while pancreatic juice flows into the intestine, but rather that the rise in total amylase in lymph is due to increase in lymph flow during pancreatic stimulation. This interpretation does not fit the data reported here. In the patient fed only fat for two days, and then tested with secretin, lipase and amylase concentration in lymph rose to extremely high levels even though rate of flow did not change significantly.

The concept that lymph from the pancreas plays a role in fat transport from the intestine is supported by several factors: 1) fats take a unique and roundabout pathway to the blood and are mixed with pancreatic lymph before entering the subclavian vein; 2) absence of the pancreas (pancreatectomy) prolongs lactescence of serum; [4] 3) episodes of acute pancreatitis are known to be associated with serum lactescence, the disappearance of which may coincide with an elevation of serum lipase.[21] It is tempting to speculate that lipase and other proteins in pancreatic lymph, conveyed to the thoracic duct, may physically or chemically change fats in such a way as to make them acceptable or able to be cleared in venous blood.

In this connection, it has been demonstrated [18] that considerable fat absorption occurs in the absence of pancreatic lipase. Further, studies in patients [13] have indicated that following a test meal of corn oil or coconut oil, the fatty acid composition of chylomicrons in thoracic duct lymph is virtually identical with that of the corn oil or coconut oil.

Following absorption of fat from the bowel, both pancreatic lipase and most of the absorbed fat, transported via thoracic duct lymph enter the subclavian vein together. Subsequent clearing of the lipemia in blood may be brought about by this lymph borne pancreatic lipase. This consideration is suggested by the demonstration that samples of thoracic duct lymph, especially those containing high lipase titers, have a clearing effect on lipemic substrates *in vitro;* this effect is enhanced by bile salts.[8] In contrast, lymph collected from patients immediately after heparin administration does not manifest lipid clearing activity, although blood serum does.[9]

Conclusions

Thoracic duct lymph has been studied in human patients with and without pancreatic disease. Experimental conditions were varied by stimulation of the pancreas with secretin; by producing sphincter of Oddi spasm with morphine; by manipulation of the pancreas at operation; and by a diet consisting only of fat. These studies have produced evidence that: 1) there is a direct functional lymphatic pathway for pancreatic secretion which transports enzymes to the thoracic duct constantly and in increased amounts during pancreatic stimulation; 2) fluid formed in the pancreas in excess of an amount which can be carried into the intestine, may be siphoned off along this lymphatic pathway; 3) efficiency of lymph flow from the gland is reduced in patients with fibrosis of the pancreas. In addition, possible contribution of pancreatic lymph to transport of fats in the thoracic duct has been discussed.

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Discussion

Dr. Oliver Cope: I come again upon the platform hoping that I do not exceed my allowance, because the subject is of such importance and this paper so interesting and timely. We have just been hearing of the undoubted significance of the lymphatic exchange and flow from the pancreas. We know that the flow of lymph from the liver is also enormous. Earlier this morning we heard about transplantation of the liver, taking the liver out and putting it back, anastomosing only the arterial venous channels. That the lymphatic channels may be completely neglected faces us with an enigma.

Physiologists have told us surgeons that the lymphatic circulation is of tremendous importance. We have known this when we came to tumor spread. This paper is so good because it begins to interest us in the secretory, the metabolic mechanisms involved. I know of only one other comparable study and that was one by Brown Dobbyns in which he showed that the thyroid hormone flows in the lymph from the thyroid to the blood stream.

We are in the infancy of our understanding of the role of lymph. Surely lymph must be important. I think this is a wonderful paper and I congratulate the authors upon their study.

Dr. John H. Mulholland (Closing): This study was undertaken to try to find why some patients who have had a number of well designed operations for pancreatitis continued to have symptoms. Implications from the study so far are discouraging in that obstruction to flow of pancreatic juice into pancreatic lymph is distal in intercellular spaces very much as obstruction to flow of lymph produces very troublesome fibrosis of the lower leg. We are not entirely discouraged and intend to pursue the problem further.

In reference to Dr. Cope's very nice remarks, I might say that Dr. Dumont and Dr. Doubilet and I think that the main pathway of secretion of insulin by the pancreas is through lymph rather than directly into the blood stream as is generally assumed. Diabetes which accompanies chronic pancreatitis is peculiar in that the islet cells are intact, and fibrosis or lymphedema may be obstructing absorption.