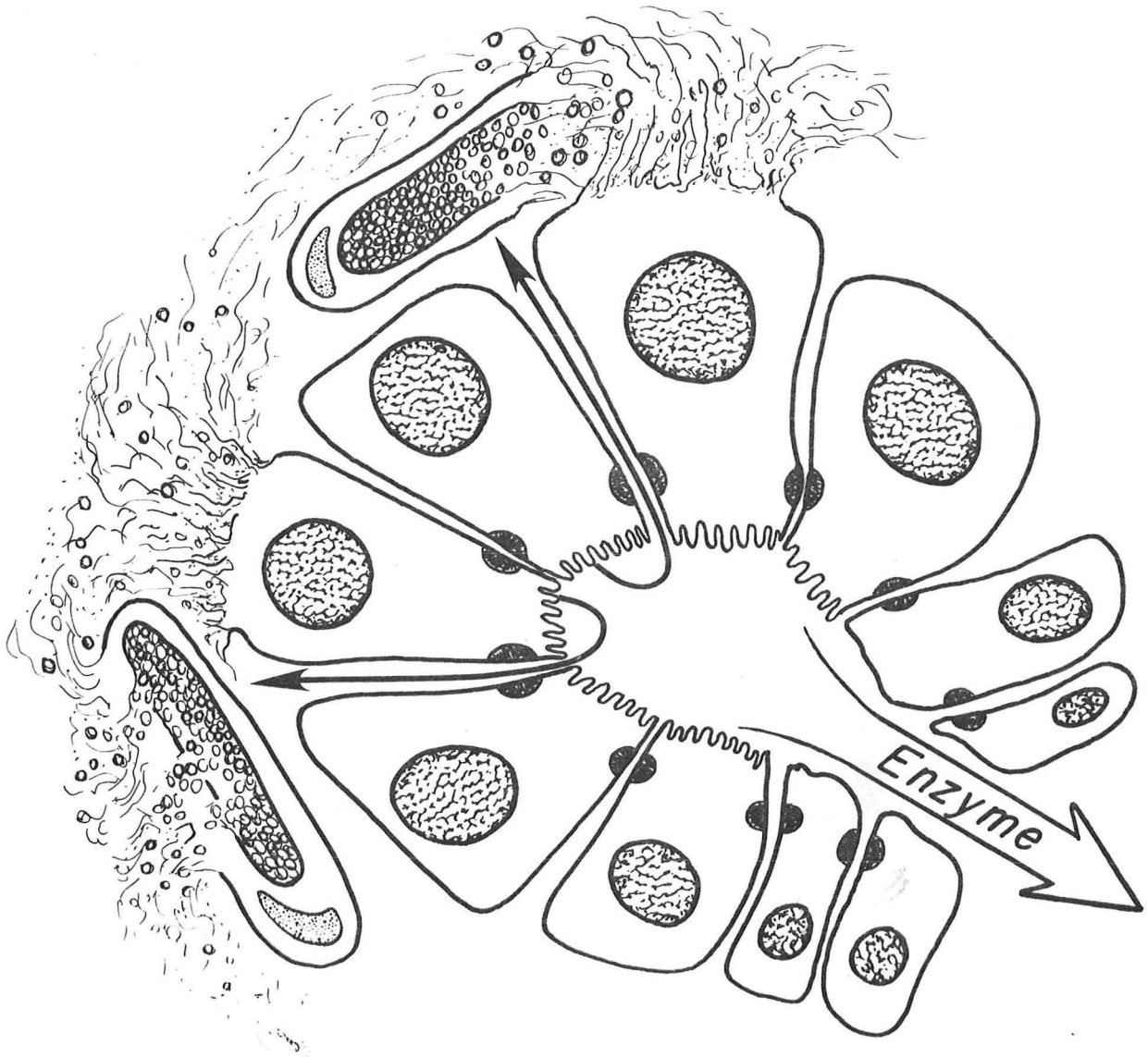
HYPERLIPIDEMIA AND PANCREATITIS



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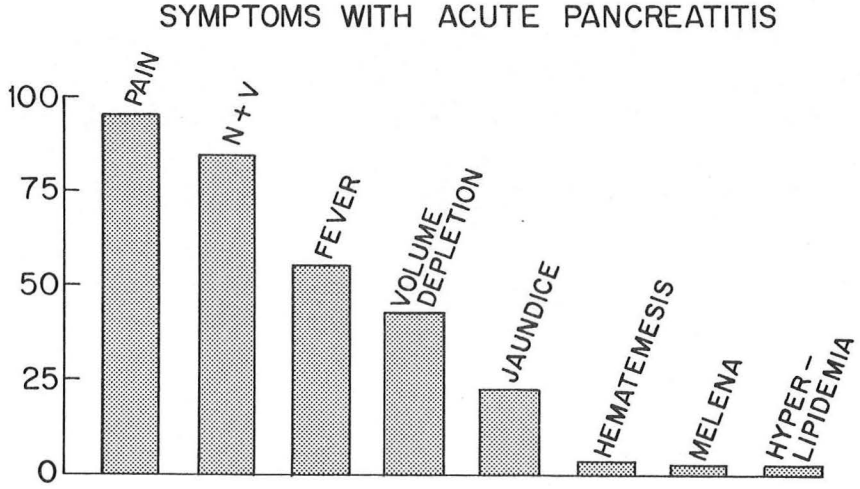
I. INTRODUCTION

Inflammation of the pancreas is a prevalent clinical entity commonly associated with excessive alcoholic intake, trauma to the abdomen, biliary tract disease, drug intake, and a number of other very diverse and apparently unrelated conditions. In the past, one of the complications of pancreatitis was said to be the development of severe hyperlipidemia. More recent data suggest that, in fact, the severe hyperlipidemia precedes the onset of the pancreatitis and, indeed, may be the cause of the development of the inflammation of the pancreas. Hyperlipidemia is most commonly associated with marked elevation in circulating chylomicrons which, in turn, may be the consequence of an underlying primary lipid disorder, diabetes mellitus, ketoacidosis, pregnancy or the intake of a number of different drugs. The possibility is reviewed in this protocol that a number of cases of pancreatitis actually result from the movement of pancreatic enzymes into the capillary vessel: if high concentrations of chylomicrons are present in the capillary blood the lipase may act on the triglyceride to release high local concentrations of free fatty acids which, in turn, promote damage to the tissue, further release of activated enzymes and the development of pancreatitis. This sequence of events is apparently most likely to occur when severe hyperlipidemia is present where the serum triglyceride levels usually are in excess of approximately 1500 mg%. Such a clinical situation appears to be most commonly encountered under circumstances where some inciting event such as heavy alcohol intake, pregnancy, oral contraceptives or diabetes is superimposed upon an underlying disorder of triglyceride metabolism.

II. THE CLINICAL FEATURES OF ACUTE PANCREATITIS

It is not the purpose of this protocol to review in detail the commonly encountered clinical features of acute pancreatitis. For a detailed discussion of these aspects of this disease the reader is referred to several references listed in the Bibliography. As shown diagrammatically in Figure 1, the cardinal symptoms of acute pancreatitis are pain associated with nausea and vomiting. Fever is present in approximately

Figure 1



half of the cases and evidence of marked volume depletion and even shock is seen. Mild jaundice is noted infrequently and gross gastrointestinal bleeding with either hematemesis or melena is uncommon. In the older literature hyperlipidemia with a grossly lactescent plasma was noted in only 2 to 7 % of the cases but in more recent publications the incidence of this finding has increased to 25-30% in some series. The true incidence of hyperlipidemia when patients are initially seen with the symptoms of acute pancreatitis is unknown since it is apparent that this finding was overlooked in the earlier series while the incidence in more recent series may be artifactually high because of deliberate selection for such patients.

Pain: In nearly all series the most common and most characteristic feature of pancreatic inflammation is the presence of abdominal pain. As shown in Table I approximately 95% of patients complain of abdominal pain.

TABLE I

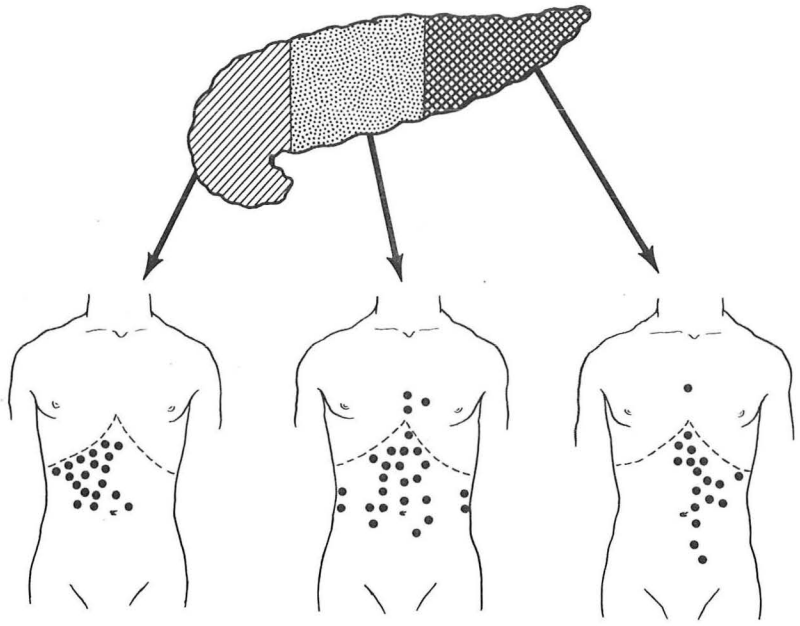
Clinical features of patients with pancreatitis

	Acute pancreatitis frequency(%)	Calcific or severely fibrosing pancreatitis frequency(%)
Pain	95	95
Mid-epigastric	77	79
Back	43*	56
Right subcostal		44
Left subcostal	30	29
Generalized	13	Rare
Retrosternal	2	Rare
No pain	5	7
Recurrent pain (with pain-free intervals)	25	76
Daily pain	0	17
Pain partially relieved by bending forward	50	58
Previous operation	-	65
Abdominal mass (cyst)	5	30
Nausea and vomiting	84	Rare
Shock	44	-
Jaundice	17	33
Alcoholism	-	25+
Loss of weight	-	100
Hematemesis	3	7
Melena	4	2
Fever	60	Rare
Diarrhea	7**	33++
Clinical diabetes	5-10	30

*Epigastric radiating to back
+United States, 75 per cent
**Acute
++Steatorrhea

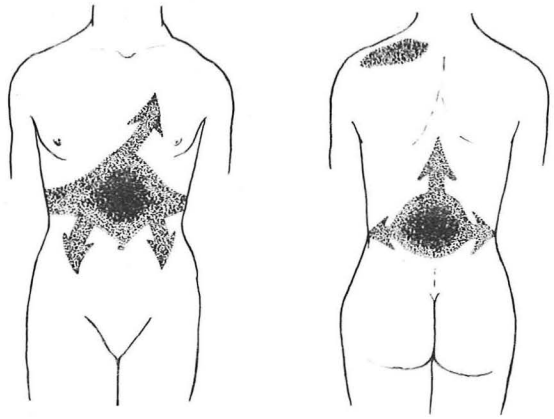
This pain is often very severe and characteristically is epigastric in location with radiation through to the low back region. Usually it is a constant severe pain that in many patients is partially relieved by leaning forward. In a minority of patients the pain may become more generalized suggesting lower abdominal pathology or may radiate upwards into the chest or even into the neck and arms. To some extent, the location of the pain probably reflects the most intense area of inflammation in the pancreas. Figure 2 shows in diagrammatic form the results of an interesting set of studies in which patients were operated on under local anesthesia and the area to which discomfort was referred was identified when different regions of the pancreas were stimulated electrically. Each dot in this diagram represents the results obtained in a single patient. As is evident, electrical stimu-

Figure 2



lation of the head of the pancreas usually resulted in discomfort in the right-epigastric region while stimulation of the mid-body of the pancreas resulted in radiation of the discomfort to either the right or left flank or upward into the substernal region. Stimulation of the tail of the pancreas caused discomfort that was always felt on the left side of the body but the specific site varied from the left lower quadrant to high in the chest and back. The most common distribution for pain seen in patients with acute pancreatitis is diagrammed in Figure 3. Most commonly patients experience the discomfort anteriorly in the mid-epigastric region but it is not uncommon for the pain to radiate anteriorly to either the right or left flank and, after the initial onset of the pain, to radiate downward to involve one of the lower quandrants. Such localization may be confusing and suggest a lower abdominal pathologic process rather than acute pancreatitis. Commonly the epigastric pain penetrates straight through to the back and is experienced in

Figure 3



the region of the lower thoracic vertebra. It may radiate up the spine in a midline location and occasionally is experienced in the left shoulder. Pancreatic pain apparently rarely is referred to the tip of the right scapula and such pain should suggest gallbladder rather than pancreatic pathology.

Nausea and vomiting: The second most common feature of acute pancreatitis is the onset of nausea and vomiting. This is probably reflex in nature and arises because of the onset of the severe pain. However a degree of ileus is commonly present in patients with acute pancreatitis and certainly may contribute to persistent nausea and vomiting. Ileus may be generalized or may be localized to those areas of the intestine that are in direct contact with the inflamed pancreas. In this latter situation one may see an isolated loop of small intestine in the upper abdomen (a "sentinal loop") or a dilated segment of transverse colon. The presence of nausea and vomiting contributes significantly to the volume loss and potassium loss characteristically seen in such individuals.

Fever: An elevation in the temperature is seen in approximately half of patients admitted with the diagnosis of acute pancreatitis. In the vast majority of these subjects there is no evidence of infection but, rather, the fever presumably is a manifestation of tissue destruction within the pancreas. Temperatures usually are in the range of 100 to 102° F but occasionally are higher and the white blood cell count is initially elevated in the range of 10,000 to 18,000.

Volume depletion: Varying degrees of volume depletion is a characteristic feature of acute pancreatitis and in a significant percent of the cases may be manifest as mild to profound shock. Such volume depletion arises from the inability of the patient to take in fluids orally, from nausea and vomiting and, most importantly, from sequestration of large amounts of fluid in the retroperitoneal region. In addition to isotonic volume loss, there may also

be variable degrees of loss of circulating of RBC mass. If there is a significant hemorrhagic component to the pancreatitis then there may be significant amounts of blood also sequestered in the retroperitoneal space and, less commonly, in the free peritoneal cavity.

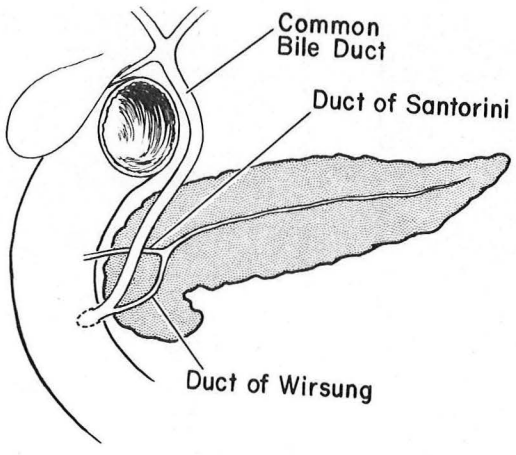
Jaundice and GI bleeding: Because of the inflammation that occurs in the duodenal C loop in patients with pancreatitis it is common to find occult GI bleeding. Much less commonly there may be duodenal erosions or stress ulcerations in the upper GI tract that results in gross hematemesis or melena. Since inflammation in the head of the pancreas may cause obstruction to the biliary outflow it is also fairly common to find mild and transient jaundice in these patients. Less commonly the degree of biliary obstruction may become more severe and prolonged and raise the possibility of some other obstructing biliary lesion.

Hyperlipidemia: The true incidence of chemical hypertriglyceridemia or gross lactescence at the onset of acute pancreatitis is unknown. Older literature suggests that this finding was seen in 2 to 7% of the cases: however, it is clear that this represents a major underestimation of this finding. More recent series have placed the incidence as high as 25% of cases: again, however, there may be bias in selection of such cases. Since variable periods of time may pass between the onset of the initial symptoms and the admission of the patient to the hospital and since hypertriglyceridemia may rapidly clear when the patient is in a relatively fasting state, it may be very difficult to ascertain the exact incidence of hypertriglyceridemia even when the physician is aware of this important finding and is actively evaluating it.

III. MECHANISMS OF PANCREATIC DAMAGE

While there is a great deal of normal variability in the anatomical relationships between the ducts draining the biliary tract and those draining the pancreas, the general features of this relationship are as shown in Figure 4. The common bile duct runs through the substance of the head of

Figure 4



the pancreas and joins the main pancreatic duct just prior to penetrating the medial aspect of the duodenal wall at the amullary region. Much significance has been attributed to the fact that the common bile duct and the duct of Wirsung join and form a common channel of variable length. Such an anatomical relationship would obviously allow for possible obstruction of the pancreatic outflow duct by stones formed in the gallbladder or for the reflux of biliary contents into the pancreatic duct. Thus, over the past 40 years, as shown in Table II, obstruction to pancreatic outflow or reflux of bile

TABLE II

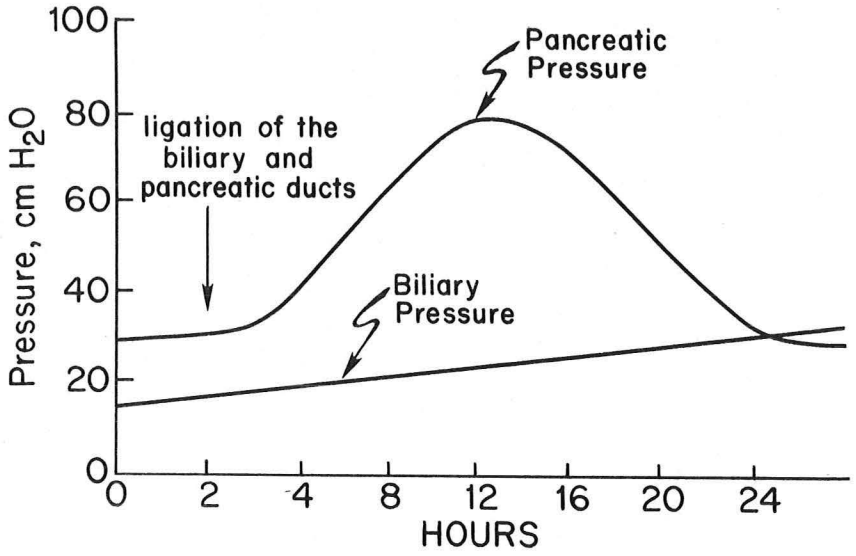
Possible mechanisms of pancreatic damage

1) Obstruction to pancreatic outflow
2) Reflux of bile into pancreatic duct
3) Reflux of duodenal contents into pancreatic duct
4) Direct toxic effect
5) Nutritional deficiencies
6) Vascular insufficiency
7) Allergic reactions

into the pancreas have been considered common causes of pancreatic damage. Other postulated mechanisms of pancreatitis have included reflux of duodenal contents into the pancreatic duct, the direct toxic effects of such substances as methanol and ethanol, nutritional deficiencies, vascular insufficiency and allergic reactions.

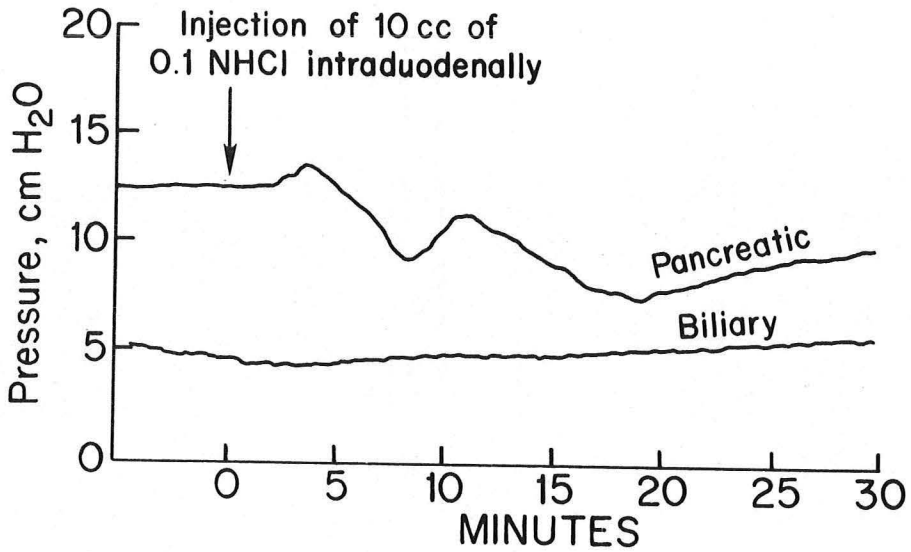
Obstruction to pancreatic outflow: For many years obstruction to the pancreatic outflow duct has been considered to be a possible important event in producing acute pancreatitis. It has been postulated, for example, that small gallstones passing down the common duct could lodge in the ampullary region causing a rise in pressure in the pancreatic duct and extravasation of enzymes in pancreatitis. However, after many years of investigation in a variety of animal species there is relatively little evidence that this mechanism is important in the production of pancreatitis in man. Occasionally patients are seen who apparently have pancreatitis secondary to an obstructing lesion (stone or cancer) in the ampullary region. This group represents a very small percentage of the total number of patients seen each year with pancreatitis. Furthermore, in several kinds of experimental animals complete ligation of the biliary and pancreatic ducts is associated with only a transient rise in the pressure within the pancreatic duct system (Figure 5) following which the pressure falls to low levels and there is progressive atrophy of the gland. In most such species, therefore, obstruction to pancreatic outflow does not result in acute pancreatitis but rather results in progressive pancreatic atrophy.

Figure 5



Reflux of bile into pancreatic ducts: A second popular theory for the cause of pancreatitis that has been extensively studied for many years is that the reflux of some biliary constituent into the pancreatic duct might lead to activation of certain of the pancreatic enzymes with destruction of the duct epithelium and inflammation of the gland. There is little doubt that acute pancreatitis can be produced by the injection, usually under high pressure, of a variety of noxious materials into the biliary tract. There is a serious question, however, as to whether any of these experimental models reflect the situation that occurs in man. For example, as shown in Figure 6, during the

Figure 6



type of stimulation that would occur when eating the pressures within the pancreatic duct are usually significantly higher than found in the biliary tract: this situation would make it difficult for free reflux to occur into the pancreas from the biliary tract. Furthermore in animal species such as the sheep, goat and rat that normally have a long common channel for drainage of the pancreatic and biliary systems spontaneous pancreatitis is virtually never seen while pancreatitis has been reported in man in individuals whose pancreatic outflow tract is totally separated from the biliary tract. After a recent extensive review of this subject White concluded that "reflux of bile as a cause of human pancreatitis recedes into the nebula of mythical nonsense".

Miscellaneous causes: As summarized in Table II, several other mechanisms have been postulated as important causes for pancreatitis. In a number of studies it has been shown that the surgical production of a closed duodenal loop can result in pancreatic inflammation and elevated circulating enzymes. This type of preparation may have relevance to those few cases of pancreatitis seen in man in which there is high small bowel obstruction or obstruction to the afferent loop following gastric surgery. However, it is unlikely that this mechanism is important in the vast majority of cases of idiopathic pancreatitis. Direct toxic effects have been suggested for such substances as methanol, ethanol or other toxins: however, generally it has been very difficult to produce significant pancreatitis in experimental animals by feeding even very large amount of ethanol. In one recent study, for example, large amounts of ethanol (the equivalent of a 10 liter intake per day in man) to rats over several months resulted in only small areas of focal necrosis in the pancreas. Nutritional deficiencies have been suggested as contributing to the development of pancreatitis, particularly in the alcoholic. However, alcoholic pancreatitis may typically occur in the younger, apparently well-nourished "binge" drinker and it is unlikely that this mechanism is important in the many cases of non-alcoholic pancreatitis. In the experimental animal vascular insufficiency, particularly when combined with obstruction to pancreatic outflow or to reflux of bile into the pancreatic duct, clearly contributes to the development of pancreatic inflammation. There is little evidence, however, that vascular insufficiency is important in most cases of human pancreatitis and, indeed, infarction of the pancreas is very uncommon. Finally, it has also been possible to sensitize various experimental animals to different types of antigens and then to produce pancreatic inflammation by injecting the antigen either into the blood supply of the pancreas or under pressure into the pancreatic duct. Once again, there is little evidence that this mechanism is important in man.

In summary, despite many years of work there is little convincing evidence that the commonly listed mechanisms shown in Table II are important either singly or in combination in producing human pancreatitis.

IV. COMMON CLINICAL ASSOCIATIONS IN PANCREATITIS

Just as the exact mechanisms operative in the production of pancreatitis are uncertain so also is the association of pancreatitis and other clinical entities. A partial list of clinical conditions that are thought to be associated with the development of pancreatitis is given in Table III. In some cases the association is definite and the reasons for development of

TABLE III

Common clinical associations in pancreatitis

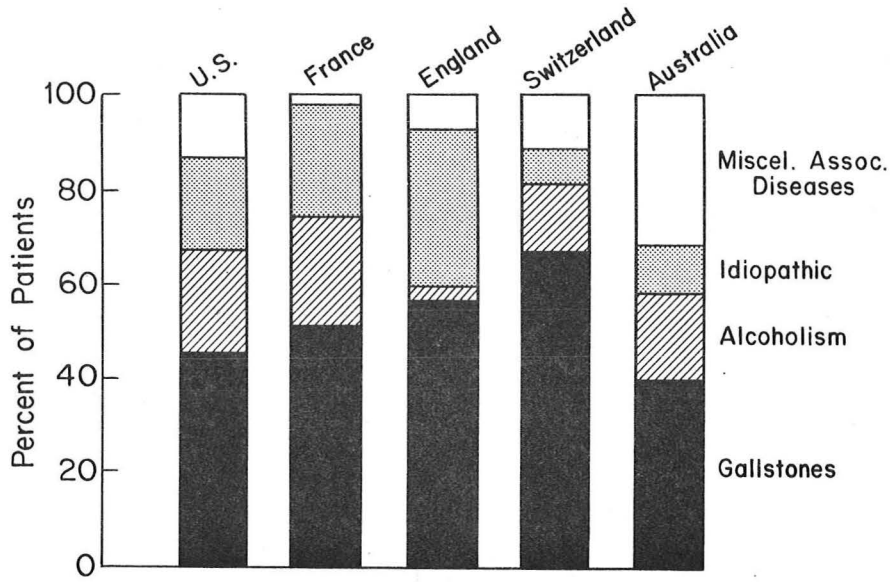
1) Biliary Tract Disease
2) Alcoholism
3) Duodenal Obstruction
4) Hyperparathyroidism and Hypercalcemia
5) Hereditary Pancreatitis
6) Primary Hyperlipidemia
7) Post Operative Pancreatitis
8) Blunt Trauma to Abdomen
9) Renal Failure
10) Nephrotic Syndrome
11) Infections:
    - Scarlet Fever
    - Typhoid Fever
    - Mumps
    - Viral Hepatitis
    - Coxsackie Virus
    - Parasitic Infestations
12) Drugs:
    - Chlorthiazide
    - Isoniazid
    - Sulfonamides
    - Indomethacin
    - Methyl Alcohol
    - Azathioprine
    - Steroids
    - Estrogens
13) Autoimmune Disease (?):
    - Systemic Lupus
    - Polyarteritis Nodosa
14) Pregnancy (third trimester and post partum)
15) Fast-Refeed or Massive Food Intake
16) Metabolic Disorders:
    - Diabetes Mellitus
    - Acute Intermittant Porphyria
17) Idiopathic

pancreatitis are probably clear. For example, following surgery in the upper abdomen in the region of the pancreas or blunt trauma to the upper abdomen it is reasonable to suppose that there has been rupture of pancreatic ducts, release of pancreatic enzymes and a secondary pancreatitis. In several other instances there seems to be a definite correlation between the presence of a particular clinical event and pancreatitis although the mechanism of interaction between these two events may be obscure: for example, pancreatitis does occur relatively frequently in patients with biliary tract disease or with heavy

alcoholic intake although, as discussed above, the mechanism of production of pancreatitis in these situations is obscure. Finally, there are a number of instances listed in Table III where the association is very questionable. For example, the association with several drugs is derived from only a few clinical reports and in these instances the patients were often ill with other disorders that might themselves have been etiological in the production of pancreatitis.

The relative importance of these clinical associations in pancreatitis in several countries is shown diagrammatically in Figure 7. In all of these countries, the populations of which are basically derived from western Europe,

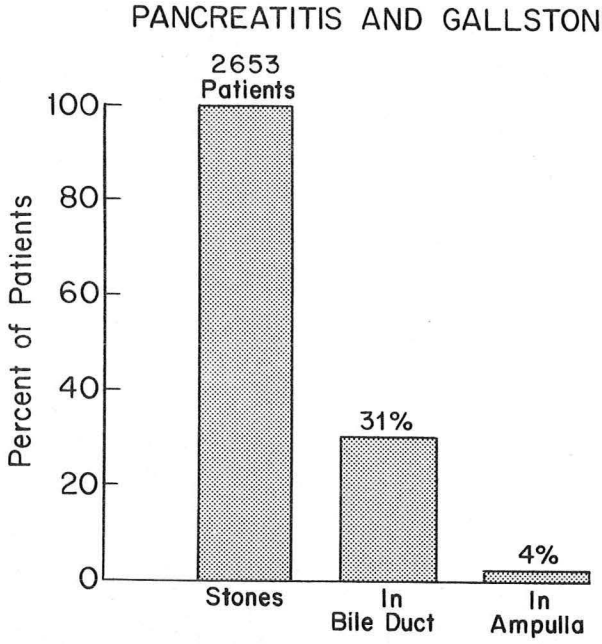
Figure 7



the most frequent finding is the association of gallstones, or at least biliary tract disease, with acute pancreatitis. Several lines of evidence support the possibility that there is a relationship between the presence of gallbladder disease (usually with stones) and acute pancreatitis. In some of the cases it has been possible to document the temporal relationship between the passage of a gallstone from the gallbladder into the intestine and the onset of acute pancreatitis. In other cases the sequence of recurrent acute attacks of pancreatitis has apparently been interrupted by removal of the diseased gallbladder. However, it is by no means certain, as suggested by the data in Figure 7, that in 40-50% of patients with acute pancreatitis gallstones are the cause of the pancreatic inflammation. It should be emphasized that gallstones are an exceedingly common disorder in western European populations so that if there were no relationship between the presence of gallstones and the onset of pancreatitis it would be expected that 15-35% of patients with pan-

creatitis would be found to harbor gallstones (depending upon the age and sex of the population under study). Furthermore, as illustrated by the data in Figure 8, in those patients with pancreatitis and gallstones only about 31%

Figure 8



have gallstones demonstrable in the common bile duct and in only 4% are the gallstones impacted in the ampulla of Vater. Thus, in the majority of cases it is difficult to understand how the presence of chronic cholecystitis and cholelithiasis could be etiologically important in the production of the acute pancreatitis. Furthermore, of some 17,717 patients who had demonstrated gallbladder disease (Table IV) only 4.8% developed pancreatitis. Thus while it seems likely that gallstones are an important cause of acute pancreatitis in some portion of the population, it seems equally probable that in a significant fraction of those patients with pancreatitis (shown in Figure 7) the presence of gallstones is only an incidental finding and the actual cause of pancreatitis is unknown.

Figure 7 also demonstrates that in most populations (with the exception of England) alcoholism is the next most common clinical condition associated with acute pancreatitis. While this association seems well supported by the clinical literature it should be emphasized that only a relatively small percentage of individuals who drink heavily actually develop pancreatitis. Since alcohol feeding to various experimental animals seldom produces a lesion similar to human pancreatitis the association between alcoholism and pancreatitis has not provided a significant clue as to the exact mechanism of how this association is articulated. The third most common group of cases

TABLE IV

Incidence of pancreatitis among patients with gallstones

	New York Hospital	Lyon, France	Houston, Texas Hermann Hospital	Seattle Hospitals	Total
Total number of cholecystectomies for gallstones	5500	5450	2285	4482	17,717
Patients with gallstones and pancreatitis	197 (3.6%)	332 (6.1%)	92 (4%)	233 (5.2%)	854 (4.8%)

of pancreatitis shown in Figure 7 are those identified as "idiopathic", i.e., cases of acute pancreatitis not associated with the presence of biliary tract disease, alcoholism or another recognized "cause" of this disorder. Finally, all of the other associated clinical conditions listed in Table III are seen in only the remaining 10 to 20% of cases of acute pancreatitis (with the exception of Australia).

The point to be emphasized here is that a common practice is to explain the occurrence of acute pancreatitis in terms of one of these clinical associations. Thus if a patient has pancreatitis and is found to have biliary tract disease, drinks several cocktails a day or has been administered a particular drug, then the pancreatitis commonly is attributed to the biliary tract disease, the drinking or the drug. A more critical appraisal of these data, however, suggests that in the vast majority of cases a particular clinical association is uncertain while in those which probably are valid we have little idea of the mechanism of the production of the acute pancreatitis.

V. THE ROLE OF HYPERTRIGLYCERIDEMIA IN PANCREATITIS

The major question to be explored in this protocol, therefore, is the possibility that a marked elevation in the serum triglyceride level is a direct cause of pancreatitis and that many of the clinical conditions associated with the development of pancreatitis do so because they produce hypertriglyceridemia. Thus, such diverse clinical conditions as diabetic

TABLE V

Relationship between hypertriglyceridemia and pancreatitis

	Cause Hypertriglyceridemia	Cause Pancreatitis
Familial hyperchylomicronemia	+	+
Other familial hypertriglyceridemia	+	+
Alcoholism	+	+
Diabetes - KA Hyperosmolar syndrome	+	+
Drugs - Estrogens Others	+	+
Renal Failure	+	+
Nephrotic syndrome	+	+
Systemic lupus	+	+

ketoacidosis, renal failure, alcoholism, and the administration of estrogens are all associated with pancreatitis and, in addition, are all associated with the production of hypertriglyceridemia. It is conceivable, therefore, that the common factor responsible for the production of pancreatitis in many of the diverse clinical conditions listed in Table III is the presence of a severe hyperlipidemia. This possibility is further supported by the relationship shown in Table V: listed in this table are a diverse number of disorders that are known to produce either a primary or secondary hypertriglyceridemia. This same group of clinical disorders is also known to be associated with the production of pancreatitis as shown in Table III.

The association of pancreatitis and severe hypertriglyceridemia is further illustrated by the following three cases:

CASE 1

The first case is that of a 28 year old woman who was admitted to the hospital because of the onset of severe abdominal pain, nausea and vomiting. Prior to 2 years before this admission to the hospital the patient had not experienced serious illnesses. Specifically there was no evidence of myocardial disease or unusual skin lesions. There was also no significant family history of atherosclerosis in the patient's 2 siblings or in other close relatives. Two and one-half years prior to admission the patient began taking oral contraceptives. Approximately 2 years prior to admission the patient experienced her first episode of abdominal pain which began abruptly and which was associated with nausea and vomiting. She was seen by her local physician for this episode and was treated with a number of unknown medications but eventually recovered after approximately a one week illness. A second similar episode occurred approximately 8 months prior to admission. After recovery from the acute episode of pain, nausea and vomiting she was evaluated by her physician who found no evidence of biliary tract disease or abnormalities on upper gastrointestinal Xray series. Renal function also was noted to be normal. The third episode of pain began 2 days prior to this admission.

At the time she was first seen in the emergency room she was found to have grossly lactescent serum and a serum triglyceride level that eventually proved to be 5200 mg%. She had upper abdominal pain with tenderness to palpation, a vague epigastric fullness and evidence of volume depletion. The white count was mildly elevated and initial serum amylase determinations were normal although these were found to be abnormal following serial dilution of the plasma.

CASE 2

The second case is a 47 year old man who has had a modest history of alcoholic intake in the past. He had worked regularly, however, and did most of his drinking on weekends and, as far as is known, never had any complications. Approximately one month prior to admission to the hospital he lost his job and had a number of marital problems. Because of these social problems he became despondent and began to drink heavily and continuously. This continued for approximately 3 weeks until 2 days prior to admission when he suddenly developed severe upper abdominal pain, and some vomiting. Nevertheless, he apparently continued drinking as much as possible. On the day of admission relatives called the police who brought him into the emergency room delirious, jaundiced and in shock. While stool examination was positive for occult blood there was no evidence of massive gastrointestinal bleeding. The liver was massively enlarged, soft and apparently tender. Immediately after admission the serum was found to be grossly lactescent, the amylase level was normal, bilirubin was 8.5 mg% and SGOT equalled 350 U. By the third day of hospitalization the lipemia had cleared significantly and the serum amylase values reached 870 U. Despite intravenous fluids, nasogastric suction, etc. the patient developed evidence of progressive liver and renal failure and died: at autopsy there was massive destruction of the pancreas and severe fatty infiltration of the liver.

CASE 3

The third case is that of a 38 year old obese woman who was said to be a diabetic. While the patient had generally been in good health she had been significantly overweight since childhood. Approximately 6 years prior to admission she was found to have a mild elevation of blood sugar and was diagnosed as having adult onset diabetes. She had no major complications of her diabetes including diabetic ketoacidosis. However, approximately 3 to 4 years prior to this admission she had begun to have recurrent episodes of abdominal pain, nausea and vomiting. These episodes would come on at intervals, would last for 3 to 6 days and would then spontaneously subside. With these episodes she would generally go to bed for 3 to 4 days, stop eating and take only liquids. Because of these recurrent painful episodes she visited her private physician who found that she had a normal upper gastrointestinal series except for gallstones. A cholecystectomy was performed approximately 2 years prior to admission but she continued to have the acute painful episodes. She was admitted to the hospital on this occasion with the sudden onset of upper abdominal pain, nausea and vomiting and was found to have a serum triglyceride level of 3700 mg% and a serum amylase value of 1500 U. She was treated for acute pancreatitis. No further evaluation was carried out but a subsequent plasma electrophoresis was said to show a "type IV" lipoprotein pattern.

Thus, in summary, while these 3 cases are very different in terms of the type of patient involved and the past history of clinically related events, they do emphasize the important relationship between severe hypertriglyceridemia with a grossly lactescent plasma and the development of significant, and in one case fatal pancreatitis.

VI. ASPECTS OF NORMAL LIPOPROTEIN METABOLISM

Before examining in detail the relationship between the presence of hypertriglyceridemia and pancreatitis it is necessary to review several relevant and important aspects of normal lipoprotein metabolism in man. This review will focus on the metabolism of chylomicrons and very low density lipoproteins and the reader is referred to several major works listed in the Bibliography concerning additional details of the metabolism of low and high density lipoproteins. As shown in the first column of Figure 9, lipoproteins

Figure 9

CLASS	MAJOR LIPID	DENSITY	S_f	Electrophoresis
CM	TG	<1.006	> 400	Origin
VLDL	TG	<1.006	12 – 400	β
LDL	Choles.	1.006-1.063	0 – 12	pre β
HDL	Choles.	1.063-1.230	—	α

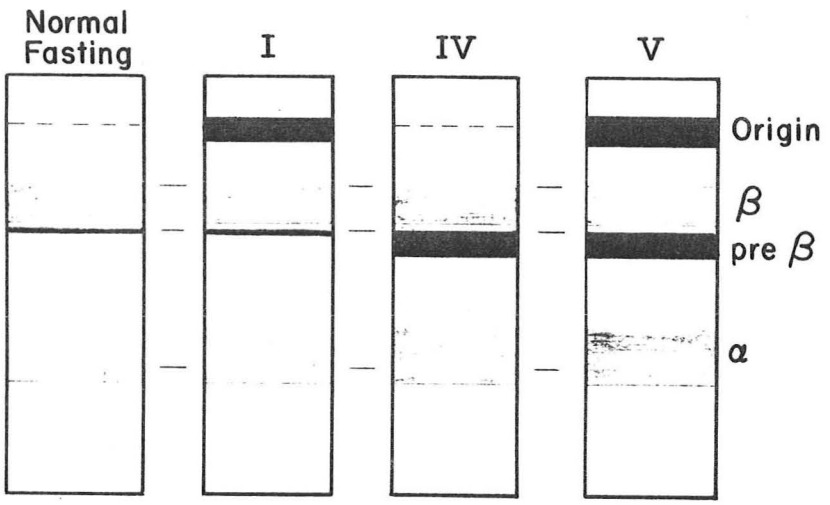
are conventionally divided into 4 major groups: chylomicrons (CM), very low density lipoproteins (VLDL), low density lipoproteins (LDL) and high density lipoproteins (HDL). Each of these major classes of lipoproteins contains varying amounts of all of the major plasma lipids including triglyceride, phospholipid, unesterified cholesterol, free cholesterol and the various peptides. However, the major lipid constituent present in each class varies markedly. Most of the chemically measureable plasma triglyceride is carried in either chylomicrons or in very low density lipoproteins. For example, > 90% of the weight of the chylomicron and > 80% of the weight of the VLDL particle is made up of triglyceride. These particles also contain much lower amounts of free and esterified cholesterol, phospholipid and various peptides. In contrast, the majority of the chemically measurable serum cholesterol is carried in either the LDL or HDL fractions. In addition to cholesterol, however,

these higher density lipoproteins also contain substantial amounts of phospholipid and protein but very low quantities of triglyceride. Because of the marked differences that exist in the relative amounts of triglyceride (density 0.90) and protein (density > 1.2) the average density of each of these classes of lipoproteins differs markedly. The average density of plasma (after the major serum proteins have been removed) is approximately 1.006. Since both chylomicrons and VLDL consist primarily of triglyceride the density of both of these particles is < 1.006. Thus, when plasma is spun in a high speed centrifuge the chylomicrons and VLDL will be less dense than the ambient electrolyte solution of plasma and so will float to the top of the tube forming a distinct layer of creamy lipid. Since LDL and HDL contain relatively greater amounts of protein the average density of these particles is higher so that the density of the ambient solution must be increased with a solute such as potassium bromide before these particular lipoproteins will float to the top of the tube. Conventionally LDL is that group of lipoproteins that move to the top of the centrifuge tube when the density of the ambient solution has been adjusted between 1.006 and 1.063 while HDL is that class of lipoproteins that floats in a density range between 1.063 and 1.230. As shown in the fourth column of Figure 9, the speed at which these various particles float to the top of the centrifuge tube varies markedly and is described in terms of the flotation number (S_f). Chylomicrons move very rapidly to the top of the tube and so have high flotation numbers, conventionally > 400, while VLDL moves more slowly to the top of the tube and conventionally has lower flotation numbers in the range of 12 to 400. Since the rate at which a particular particle floats to the top of a specimen tube is a function of the centrifugal force applied, the time of centrifugation and the flotation number this difference in S_f values between chylomicrons and VLDL has an important clinical consequence. Since the flotation number for chylomicrons is so high the exposure of a tube of plasma to a force of 1 G for 12 hours is sufficient to bring most chylomicrons to the top of the tube as a distinct creamy layer. In contrast, VLDL require the application of a much greater G force in order to produce significant layering so that these particles remain uniformly dispersed in a tube of plasma allowed to sit in a refrigerator for even 24 hours. Thus a few bedside observations provides considerable information as to the presence or absence of abnormal amounts of these lipoproteins. If a freshly drawn plasma sample is milky appearing, i.e., manifests lactescence, then either chylomicrons or VLDL levels must be elevated. Elevations of LDL and HDL do not cause lactescence. If a tube of plasma is then allowed to stand upright in a refrigerator for 12 to 24 hours layering of all of the lactescent material at the top of the tube indicates a major elevation of the chylomicron fraction while persistence of uniform dispersion of the lactescence strongly suggests an elevation of the VLDL fraction.

Another commonly utilized laboratory procedure for the identification of these various types of lipoproteins involves electrophoresis of plasma follo wed by staining of the lipid components. As shown in the right column of Figure 9 in the usual electrophoretic system chylomicrons remain at the origin, while LDL and HDL migrate away from the origin into the β and α lipoprotein regions, respectively. VLDL moves as a narrow band just ahead of the β band and hence is commonly referred to as the "pre β lipoproteins". In the past, a classification system for the hyperlipoproteinemias evolved based upon certain characteristic electrophoretic patterns: it is now known

that this classification system is inadequate and does not identify specific genetic lipid disorders (see Bibliography). Nevertheless this typing system is still utilized as a "short-hand" method for describing certain characteristic lipid disorders in the plasma. Those which are important to the present discussion are summarized diagrammatically in Figure 10. Normal fasting

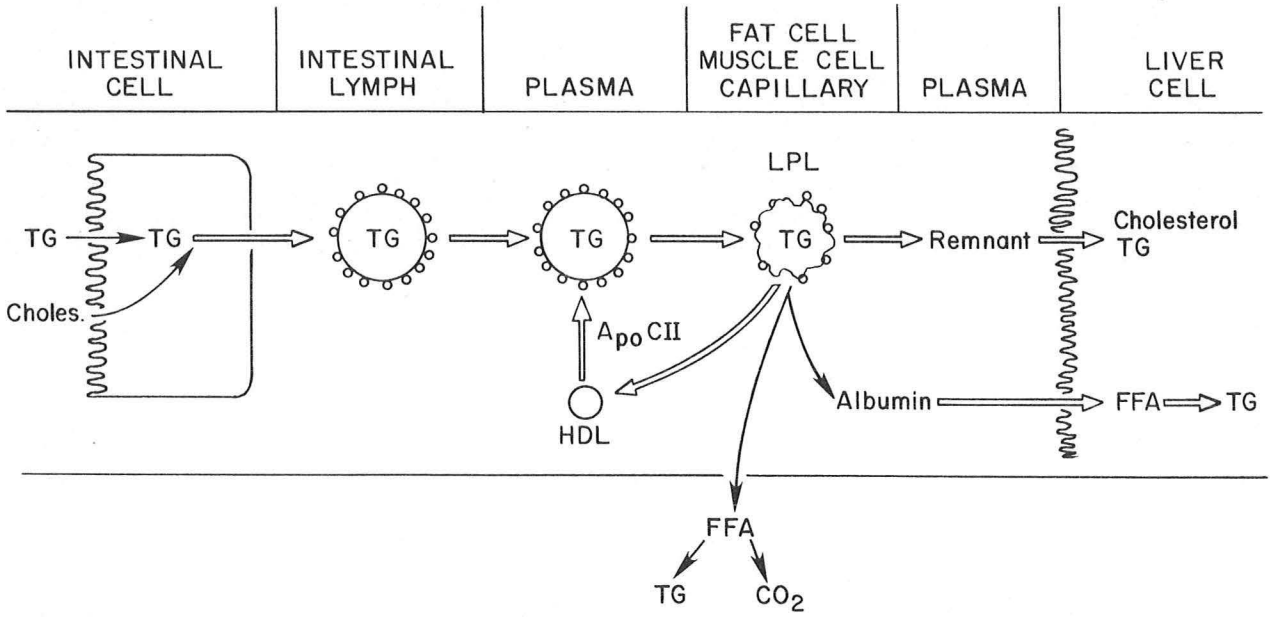
Figure 10



plasma contains no chylomicrons and shows a definite α and β band and a faint pre β band corresponding respectively, to HDL, LDL and VLDL normally present in such plasma. A type I pattern shows a densely staining band at the origin while a type IV pattern shows a densely staining pre β band. These patterns indicate, respectively, an abnormal elevation of chylomicrons and VLDL particles in the fasting state. Some patients have abnormal elevations of both VLDL and chylomicrons in fasting plasma resulting in the typical type V pattern also shown in Figure 10. It should again be emphasized that these patterns are only the phenotypic manifestation of a variety of different diseases and do not represent discreet disease entities.

Of these 4 major lipoprotein classes 2 are relevant to the present discussion: chylomicrons and very low density lipoproteins. The normal metabolism of the chylomicron particle is summarized in Figure 11. Following the normal daily intake of approximately 100 g of dietary triglyceride and 1-2 g of dietary cholesterol the lipids are absorbed into the intestinal epithelial cell and are synthesized into the chylomicron particle. This particle is essentially a core of triglyceride in which is also dissolved cholesterol esters surrounded by surface active components such as phospholipid, unesterified cholesterol and several types of apoproteins including apo C, apo B and apo A. The completed chylomicron particle is then released by an exocytotic process from the base of the intestinal epithelial cell and is swept into the central lacteal of the intestinal villus and hence eventually reaches the thoracic duct. The chylomicron found in the lymph, however, is still relatively deficient in a number of apoproteins, particularly in the lower molecular weight apo C apoproteins and so is commonly referred to as the "nascent chylomicron" particle. Once this particle reaches the circulation,

Figure 11

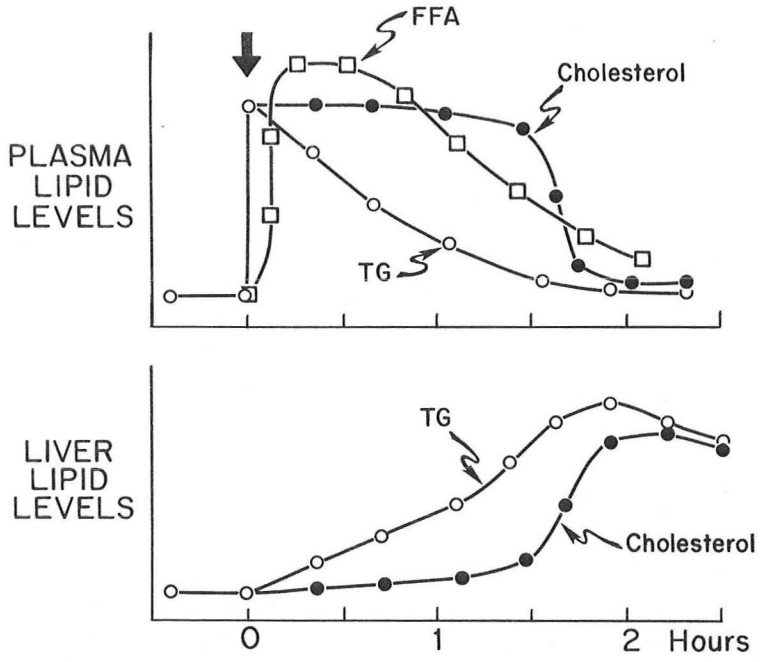


however, additional amounts of apo C are transferred to it from high density lipoproteins. One of the C apoproteins, i.e., apo C II, is particularly important since it is a potent activator of lipoprotein lipase activity. The "mature" chylomicron with its complete compliment of apoproteins then circulates through the body reaching the capillary beds in the heart, in peripheral muscles and in adipose tissue. Within this microenvironment lipoprotein lipase, an enzyme probably bound to the surface of the capillary endothelium, hydrolyzes the triglyceride in the core of the chylomicron releasing large amounts of free fatty acids. A portion of the released fatty acids will be bound to albumin and escape into the general circulation but a very significant portion of it will diffuse down the existing activity gradients between the lumen of the capillary and the cytosolic compartment of the surrounding cells. In the heart and in other muscles this free fatty acid will be activated and oxidized as a major source of energy. In adipose tissue (in the fed state) much of the free fatty acid will be re-esterified to triglyceride and stored in the adipocyte. After a variable amount of triglyceride has been removed from the chylomicron particle it is known as a "remnant". This chylomicron remnant contains most of the cholesterol originally present in the chylomicron but relatively little of the original triglyceride. Another very important point is that the liver cell now "recognizes" the chylomicron remnant and rapidly transports it, apparently intact, into the hepatocyte. As a consequence of these complex interactions the majority of dietary triglyceride originally absorbed from the gastrointestinal tract finds its way into the peripheral fat and muscle tissue while the majority of the dietary cholesterol is delivered directly to the liver. A small portion of the dietary fatty acids does, however, also reach the liver either as the residual triglyceride carried in the chylomicron remnant or by hepatic uptake

of free fatty acids from the plasma (as diagrammed in Figure 11).

These various steps involved in the normal metabolism of chylomicrons can be readily demonstrated in the experimental animal by following the levels of various lipid components in the plasma. Representative data are shown in Figure 12. At time zero (the arrow in the upper panel) it is assumed that a bolus of chylomicrons was quickly injected into the vascular space.

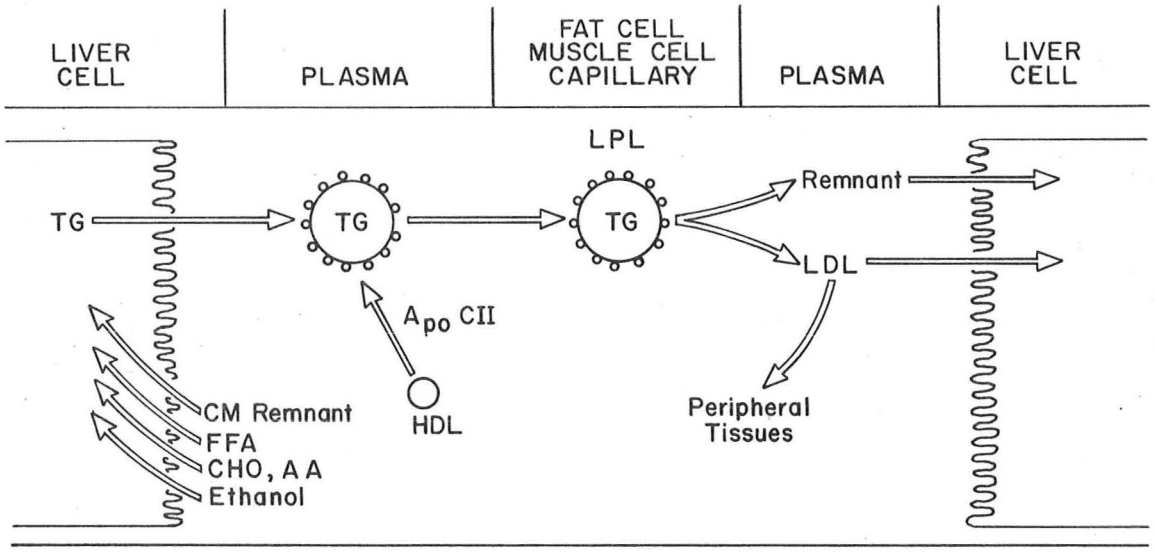
Figure 12



This results in an abrupt increase in both the serum triglyceride and cholesterol levels. As shown in the upper panel there is a rapid and striking increase in the plasma free fatty acid levels and a gradual decline in the plasma triglyceride levels reflecting, presumably, the hydrolysis of triglyceride by lipoprotein lipase in the peripheral fat and muscle tissues. The plasma cholesterol level, however, does not change significantly during this hydrolysis phase until remnant formation has apparently occurred: at this point there is a sudden decline in plasma cholesterol levels and a sudden increase in the level of cholesterol in the liver as the chylomicron remnants are very rapidly taken up in to the hepatocytes. Thus, to summarize, the chylomicron is synthesized within the intestinal epithelial cell, receives additional apoproteins by interaction with circulating HDL, is depleted of its triglyceride content in the peripheral muscle and adipose tissues and is finally taken up and destroyed within the hepatocyte. From these considerations it is apparent that abnormal elevations of chylomicrons might be induced by a very high fat diet (an ineffective way to produce hyperchylomicronemia) by a relative deficiency of apo C II, by ineffective or absent lipoprotein lipase activity or, possibly, by defective remnant clearance by the liver.

The metabolism of the second triglyceride-rich particle, the very low density lipoprotein, is summarized in diagrammatic form in Figure 13. In contrast to the chylomicron the VLDL particle is synthesized in the liver cell. The liver continuously accumulates fatty acids from a variety of sources. For example, lipid will reach the liver in the chylomicron remnant

Figure 13



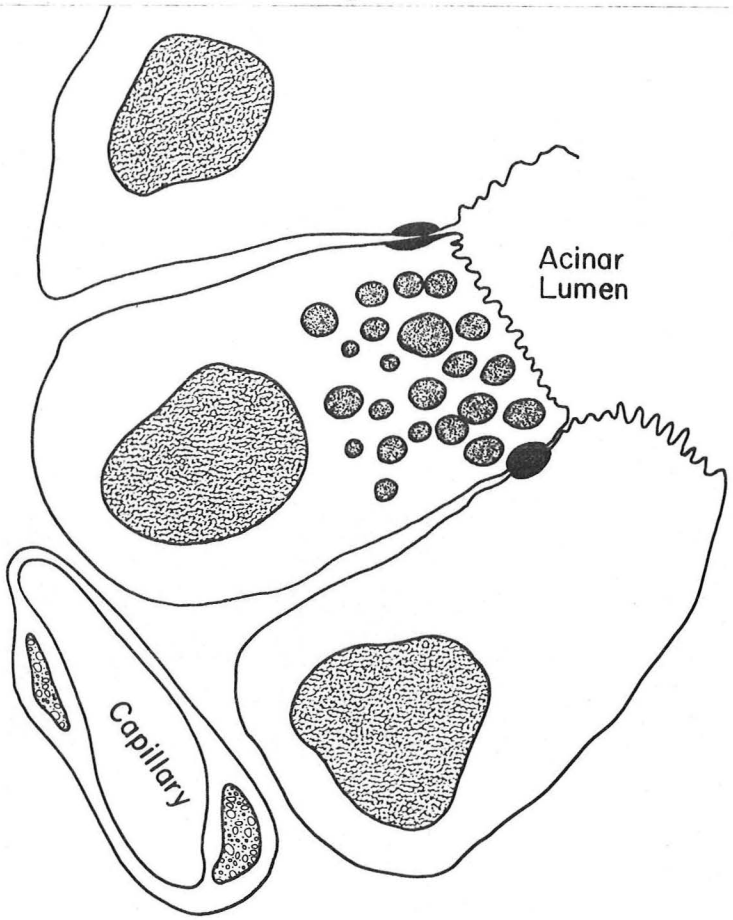
or by uptake of plasma free fatty acids. In addition, ingested carbohydrates, amino acids or ethanol may be metabolized to acetyl CoA which, in turn, is utilized for the synthesis of long chain free fatty acids. Regardless of the source, a portion of these free fatty acids is rapidly re-esterified to form triglyceride: these triglyceride droplets are then coated with a layer of phospholipid, free cholesterol and specific apo lipoproteins and are then secreted into the sinusoidal space by an exocytotic process. As was true of the nascent chylomicron particle such newly synthesized VLDL particles also are apparently deficient in certain apoproteins and, in particular, require additional amounts of apo C II from interaction with circulating HDL particles. Such particles are then metabolized in the peripheral adipose and muscle tissue by lipoprotein lipase in a manner entirely analogous to that described for chylomicrons. The products of this metabolic process, however, are significantly different from those that result from the metabolism of the chylomicron. Apparently a "VLDL-remnant" also is formed which is rapidly cleared by the liver. However, a major portion of the VLDL particles (in man, at least) undergo metabolic alterations leading to formation of the low density lipoprotein. Thus, current information suggests that the major source of circulating LDL in man is through the synthesis and metabolism of VLDL particles. The LDL then carries its cholesterol component to the peripheral tissues where it is taken up and metabolized as described in detail by Brown and Goldstein. A portion of the LDL is also transported into the liver: the rate of cholesterol uptake by the liver, however, from LDL is

of the order of 10 to 20 times slower than the rate of uptake of cholesterol carried in the chylomicron remnant. In summary the very low density lipoprotein particle is synthesized in the liver cell and functions to transport both triglyceride and cholesterol out of the liver to the peripheral tissues. In theory, abnormal elevations of VLDL could result from excessive uptake of free fatty acids, carbohydrate or ethanol by the liver or by defective degradation of this lipoprotein particle in the plasma.

VII. POSSIBLE MECHANISMS OF CHYLOMICRON (AND VLDL) -INDUCED PANCREATITIS

There is an accumulating body of evidence which suggests that pancreatitis is produced when pancreatic enzymes, particularly pancreatic lipase, hydrolyzes triglyceride carried in chylomicrons (and possible VLDL) liberating large concentrations of free fatty acids within the capillary bed of the pancreas. Figure 14 is a diagrammatic representation of an electron photomicrograph of the pancreatic acinar region. The acinar epithelium is made up of highly polarized epithelial cells which contain a large basally located nucleus surrounded by a densely packed endoplasmic reticulum (not shown in this diagram). Secretory granules of varying size and density are typically

Figure 14

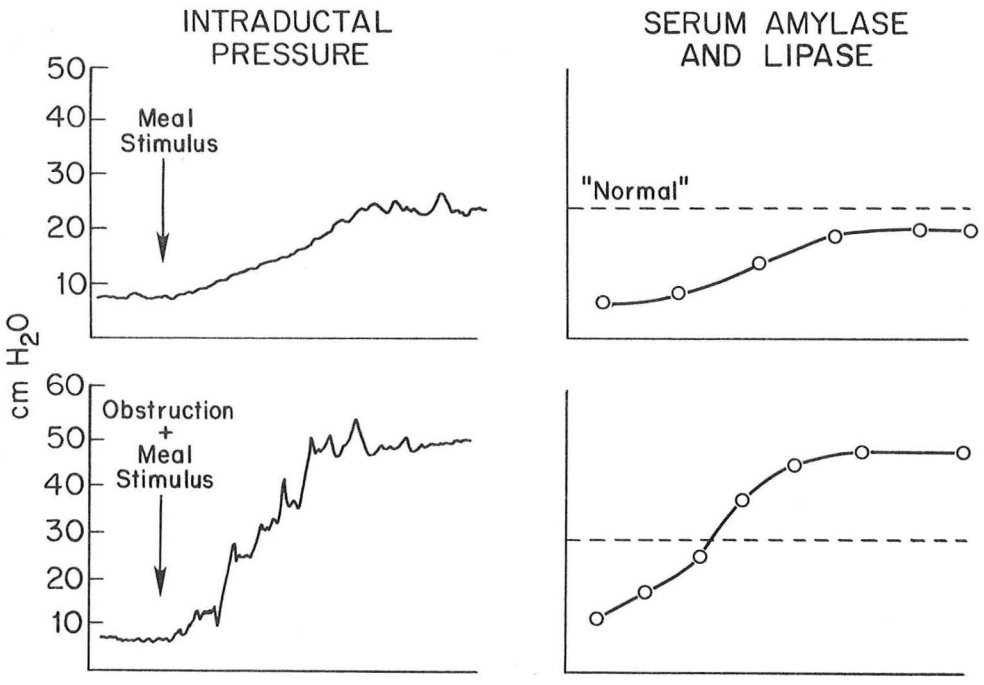


scattered throughout the apical portion of the cell and the enzymes contained in these granules are secreted into the acinar lumen across the microvillus border of the apical portion of the cell. Adjacent cells in the secretory epithelium are held together near the apical border by a junctional complex. The capillary of the pancreas is immediately juxtapositioned to the basalar portion of the secretory cells. From this anatomical arrangement it is apparent that pancreatic enzymes secreted into the acinar lumen could theoretically backflux through the junctional complex and reach the intercellular space and the capillary lumen. If such an event took place and if, for example, active pancreatic lipase reached the lumen of the pancreatic capillary under circumstances when significant triglyceride levels were present because of elevated circulating levels of chylomicrons, then significant triglyceride hydrolysis in free fatty acid release might occur.

There are several lines of evidence that support the conclusion that under normal physiological circumstances there is indeed reflux of pancreatic enzymes into the pancreatic vascular bed. For example, even in the fasted, unstimulated state there are measurable quantities of both lipase and amylase activity in the plasma. In the case of the amylase activity modern separatory techniques such as chromatography on DEAE-sephadex A-50 and isoelectric focusing have resolved the activity into isoenzymes apparently arising in both the salivary gland and in the pancreas. While the exact proportion of the amylase activity found in plasma from fasting subjects that arises from the salivary gland versus the pancreas is still unsettled, it is likely that in the fasting state pancreatic enzymes do reach the vascular space.

Under physiological circumstances where pancreatic secretions are stimulated there is little doubt that this process occurs. As shown in the left-uper panel of Figure 15, following the intake of a meal (such a "meal stimulus"

Figure 15



could be induced experimentally by actually feeding a meal, by instilling acid into the duodenal loop or by administration of secretin-pancreazymine preparations) there is a rise in the intraductal pressure in the pancreas. This is associated with a slight rise in circulating amylase and lipase levels (right panel) although in normal individuals without evidence of pre-existing pancreatic disease or biliary obstruction these values usually never rise above the "normal" levels set by the clinical laboratories in most hospitals. However, as shown in the lower panels of Figure 15, if the pancreas is stimulated under circumstances where there is intraductal obstruction or ampullary spasm the pressure within the main pancreatic ducts arises much higher and in the majority of even normal individuals there will be a significant rise in the level of pancreatic enzymes in the plasma. Thus, for example, the simultaneous administration of morphine (to increase the tone of the ampulla) and secretin (to stimulate pancreatic flow) will elevate the serum amylase level in approximately 70% of people without evidence of pancreatic disease. Taken together, these various observations strongly suggest that pancreatic enzymes secreted into the acinar lumen rather routinely regurgitate into the capillary blood of the pancreas in the fasting state and, in particular, under circumstances where pancreatic outflow is stimulated and intraductal pressures increase.

These observations certainly support the possibility that a number of pancreatic enzymes routinely enter the pancreatic capillary blood. As summarized in Table VI, however, a number of pancreatic enzymes are known to be secreted in an inactive or "pro" form. The 2 endopeptidases are secreted in an inactive form and are thought to be activated only in the intestinal lumen. Pancreatic lipase also requires a co-lipase and the presence of bile acid to attain maximal enzymatic activity. However, it

TABLE VI

Activators of pancreatic enzymes

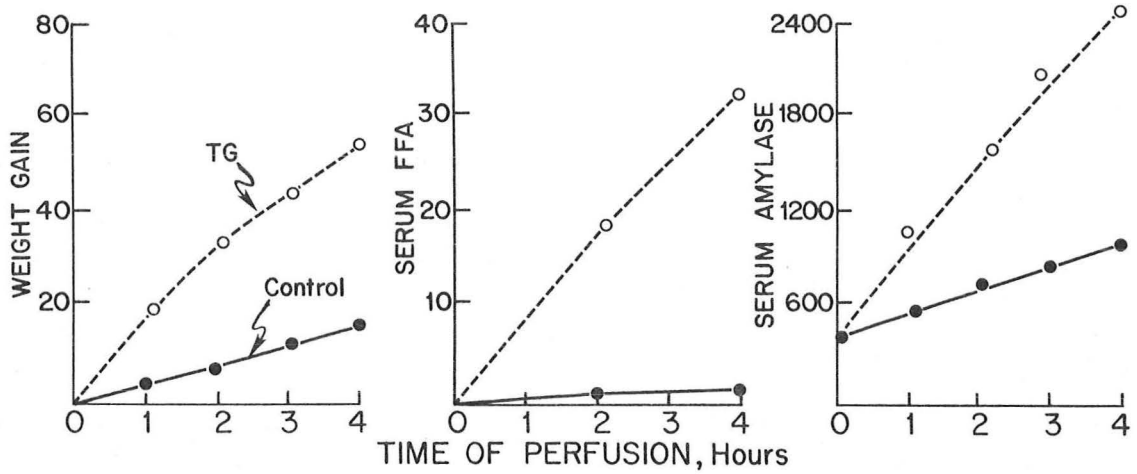
Pancreatic enzyme	Activator	Active enzyme
Trypsinogen	Trypsin, Ca^{++}, Mg^{++}	Trypsin
Chymotrypsinogen	Trypsin	Chymotrypsin
Lipase	Bile acids	Lipase
Phospholipase	?	Phospholipase
Amylase	Cl^{-}, Ca^{++}	Amylase

should be emphasized that trypsinogen and chymotrypsinogen undergo autoactivation by small amounts of trypsin and pancreatic lipase manifests significant enzymatic activity even in the absence of the co-lipase and bile acids. When these various enzymatic activites are measured in plasma of

patients it is apparent that the enzymes are active against their appropriate substrates under conditions that are very different from those physiologically encountered within the intestinal lumen. It is reasonable to suppose, therefore, that these various enzymes have at least partial activity when regurgitated into the pancreatic capillary blood.

There are several lines of experimental evidence which clearly support several of the suppositions outlined above. The studies shown in Figure 16 were carried out by Cameron and Margolis in the isolated perfused pancreas.

Figure 16

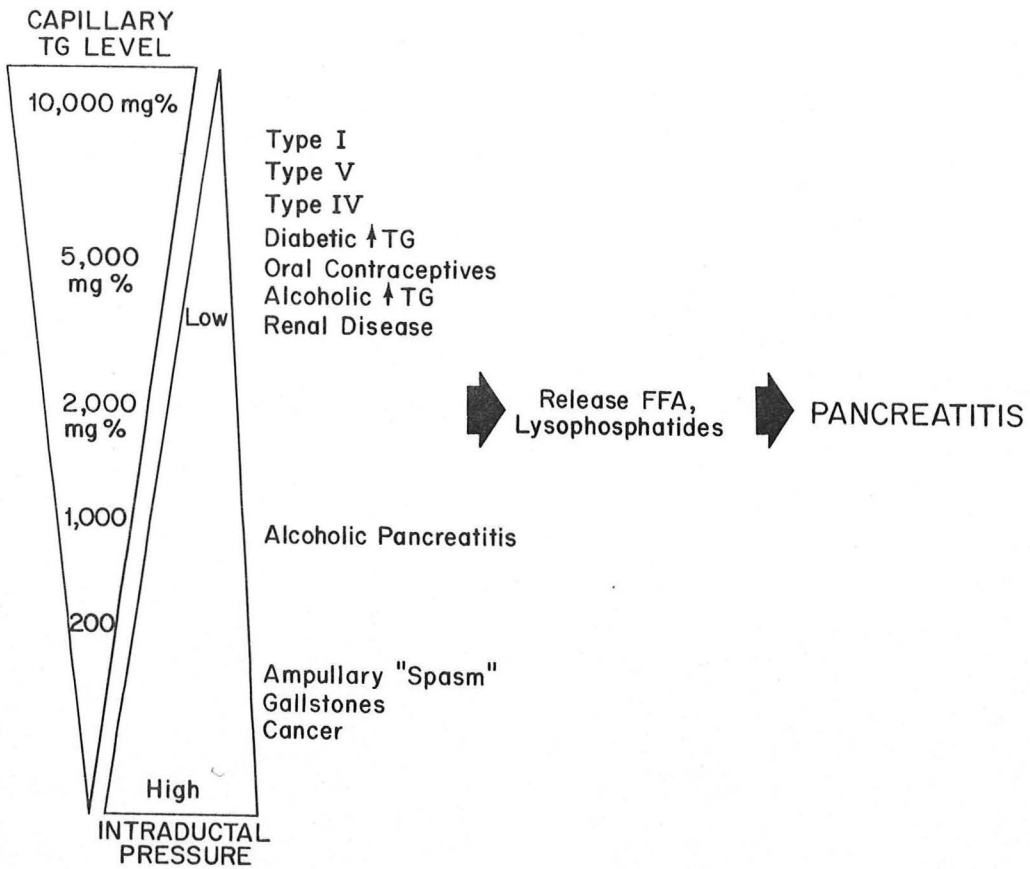


In the control situation when the pancreas was perfused with an artificial blood mixture containing a low triglyceride concentration the glands accumulated only a small amount of edema fluid (panel 1) and the concentration of free fatty acids (panel 2) and amylase (right panel) showed only small rises over the 4 hour period of perfusion. However, when triglyceride in the form of an artificial emulsion was added to the perfusate the glands became markedly edematous, as evidenced by the marked gain in weight, and there was a dramatic increase in the concentration of circulating free fatty acids. Coincident with these changes there was evidence of significant pancreatic damage as shown by the abrupt rise in the perfusate amylase concentration and by histologic evidence of tissue edema and necrosis consistent with pancreatitis. While it would be of considerable interest to repeat such studies utilizing chylomicrons or VLDL in place of the artificial triglyceride emulsion, these studies do unequivocally establish that there is very significant lipase activity reaching the pancreatic capillary bed (even in this unstimulated gland) and that the release of free fatty acids is at least associated with chemical and histologic evidence of the development of acute pancreatitis.

From these various considerations 2 conclusions are probably warranted concerning the interrelationship between the presence of severe hyperlipidemia

and the development of pancreatitis. First it is evident that pancreatic enzymes, and in particular pancreatic lipase, regurgitates from the pancreatic acinar duct into the pancreatic capillary. The rise in peripheral blood levels of these enzymes is accentuated by stimulation of the pancreas particularly if any degree of pancreatic outflow obstruction is present. If such rises are demonstrable in the peripheral circulation then it is also evident that the actual rises in enzymatic activity within the microenvironment of the pancreatic capillary are many fold higher. Second, under these conditions when a high concentration of plasma triglyceride is present in the capillary blood there is significant hydrolysis of triglyceride with the release of free fatty acids which may produce local vascular damage, additional proteolitic enzyme activation and release, and histologic evidence of pancreatitis. These observations, in turn, can be utilized to construct a hypothetical model that may explain the interrelationships between the serum triglyceride level, the pressure within the intrapancreatic outflow tract and the clinical conditions known to be complicated by acute pancreatitis. This model is shown in schematic form in Figure 17. The major thesis inherent in this model is that

Figure 17



most cases of pancreatitis, regardless of their specific etiology, are caused by an interaction of pancreatic enzymes (principally lipase) and triglyceride

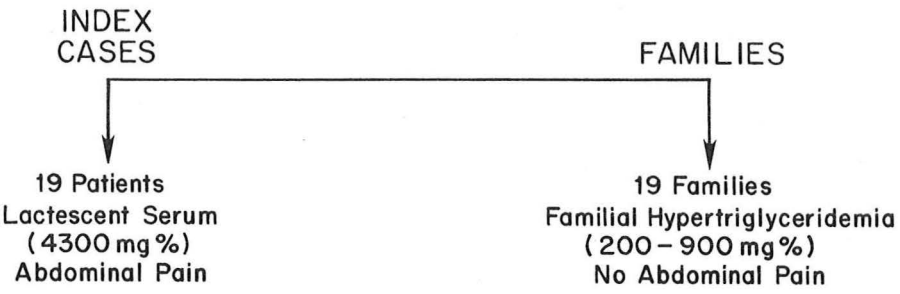
present in the capillaries of the pancreas. As illustrated by the lower part of the figure one can postulate that there are some clinical conditions such as passage of gallstones through the ampulla of Vater, obstructing cancer or ampullary "spasm" (as might occur with alcoholism and/or duodenitis) that cause high intraductal pressures and corresponding high rates of enzyme regurgitation into the capillary bed. These high enzymatic levels may lead to the liberation of locally toxic amounts of free fatty acids even under circumstances where the serum triglyceride levels are in the normal range or are slightly elevated by the dietary intake of triglyceride and the subsequent normal level of chylomicronemia. At the other extreme is a very diverse group of clinical syndromes all characterized by the production of severe hypertriglyceridemia, usually in excess of 1500 mg%, where interductal pressures might be in the normal range but where regurgitation of even "physiological" amounts of lipase activity into the capillaries releases sufficient amounts of free fatty acids to initiate acute pancreatitis. Patients that fall into this general category most commonly manifest a "type V" lipoprotein pattern and much less commonly a type I or type IV pattern. Also included in this group of patients are those who have diabetes, those with decompensated diabetes and ketoacidosis, young women on oral contraceptives containing estrogens, chronic and acute alcoholics and patients with a variety of renal lesions including those with renal failure and nephrotic syndrome. In all of these conditions the presumed initial event is the release of the locally high concentrations of free fatty acids and, possibly, lysophosphatides with local capillary and acinar damage. It is possible that other enzymes such as trypsin then come into play producing aggregation of chylomicrons, microthrombosis and further pancreatic damage through anoxia and cell destruction.

VIII. SPECIFIC TYPES OF HYPERTRIGLYCERIDEMIA ASSOCIATED WITH PANCREATITIS

Regardless of whether these speculations concerning the relationship between intraductal pressure and capillary triglyceride levels are correct, there is currently little doubt that the syndrome shown in the upper part of Figure 17 exists. Apparently patients who develop severe hypertriglyceridemia (predominantly due to an elevation of circulating chylomicron levels) run a high risk of developing pancreatitis. The converse, however, apparently is not true: in contrast to what has been taught in the past there is little evidence that pancreatitis leads to the development of severe hyperlipidemia. The difficulty in better characterizing this syndrome is that the scattered case reports involve a very diverse and apparently heterogenous group of patients. These include individuals with clear-cut inherited triglyceride disorders, patients with serious metabolic disorders such as diabetic ketoacidosis and alcoholism, patients with various renal lesions and individuals taking certain drugs, particulary drugs containing estrogens. In the past few years however, several reports have appeared in the literature where small numbers of these cases have been followed-up after recovery from the acute pancreatitis. In a number of these cases it was found that the patients had an underlying familial triglyceride disorder that was apparently accentuated by the superimposition of dietary indiscretion, alcohol or drug intake or the presence of another unrelated illness such as diabetes, renal failure or a collagen vascular disease.

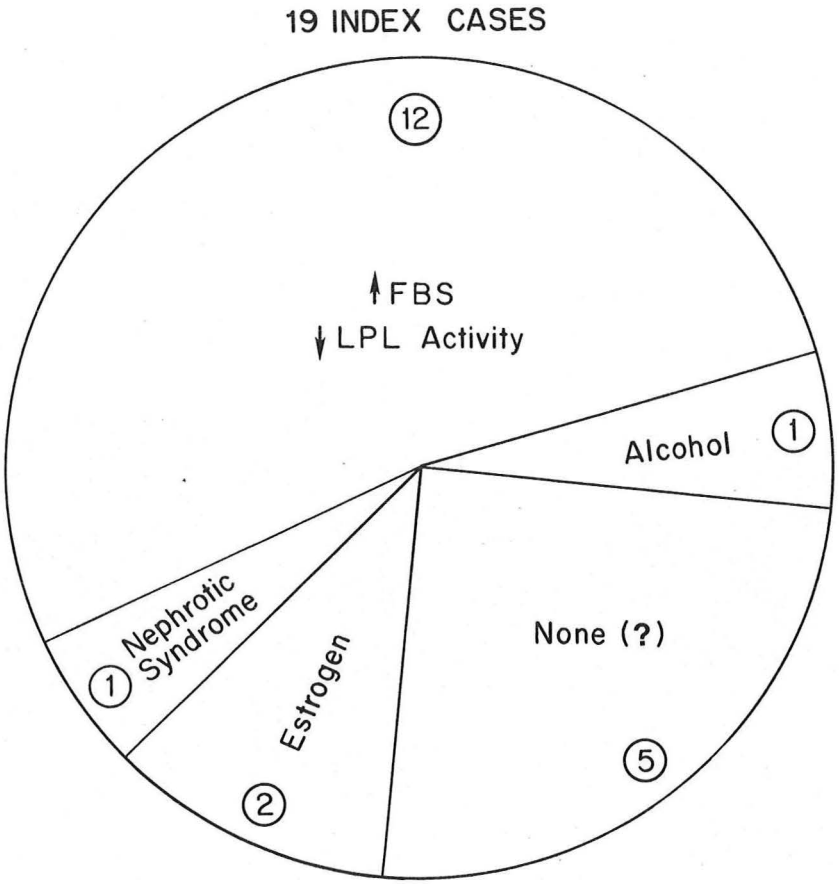
One of the largest of these recent series is that of Brunzell and Schrott and the results of this study are sumarized in Figures 18 and 19. In this

Figure 18



study 19 index cases were seen in the hospital with the syndrome of severe abdominal pain and a grossly lactescent serum: in these subjects the average serum triglyceride level was approximately 4300 mg% at the time of admission although the values ranged from approximately 900 to 10,000 mg%. When the families of these 19 index cases were examined all were found to manifest some form of familial hypertriglyceridemia: there were 65 relatives having

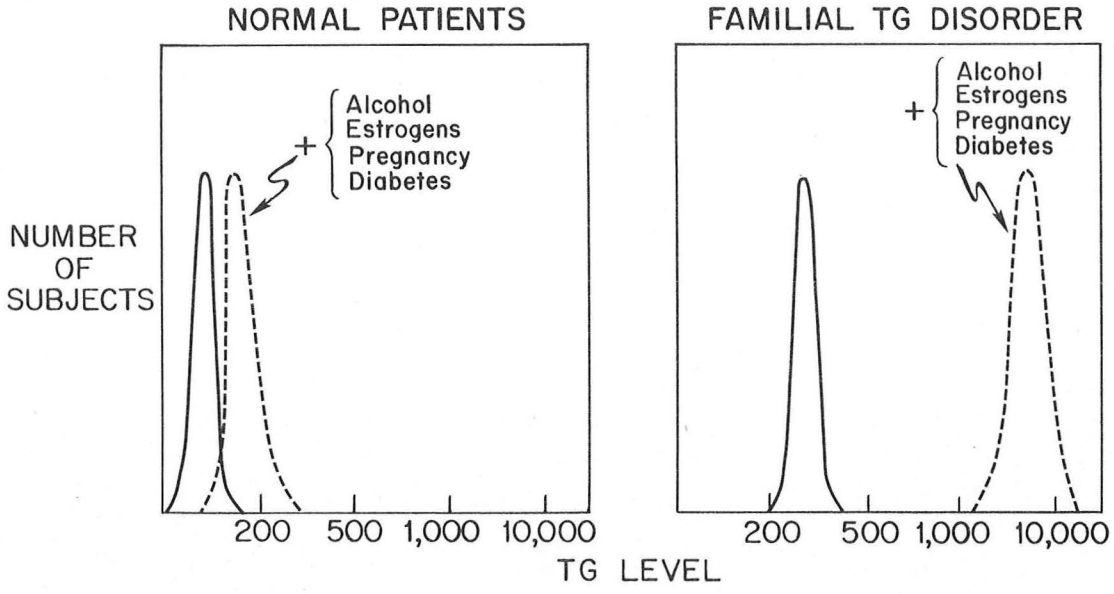
Figure 19



abnormal fasting serum triglyceride values in the range of approximately 200-900 mg%. It is important to emphasize that none of these affected relatives with only mild hypertriglyceridemia had abdominal pain or other evidence of pancreatitis. The fundamental question posed by these studies was why the index cases developed the extraordinary degree of hypertriglyceridemia. Analysis of these index cases, as shown in Figure 19, revealed that in many subjects there was a superimposed "inciting" event. Twelve of the cases were found to have diabetes mellitus and the majority of these were demonstrated to have lower than normal lipoprotein lipase activity. One of the patients had excessive alcoholic intake, two were receiving estrogens and one had the nephrotic syndrome. In 5 of the cases no specific inciting event could be identified but 2 of these cases ultimately proved to have familial hyperchylomicronemia (type I hyperlipoproteinemia). Since diabetes, alcohol, estrogens, etc. are known to induce abnormalities in triglyceride metabolism in normal subjects it was postulated that the superimposition of these "inciting" events upon an underlying familial disorder of triglyceride metabolism led to the development of the extraordinarily high triglyceride levels seen in 19 index cases. Several other smaller similar series are listed in the bibliography so that this thesis seems fairly well supported by currently available data.

This interaction between familial lipid disorders and a number of inciting events is summarized in diagrammatic form in Figure 20. As shown by the solid line in the left panel normal subjects (those not having a familial lipid disorder) usually have fasting triglyceride levels well below 200 mg%.

Figure 20



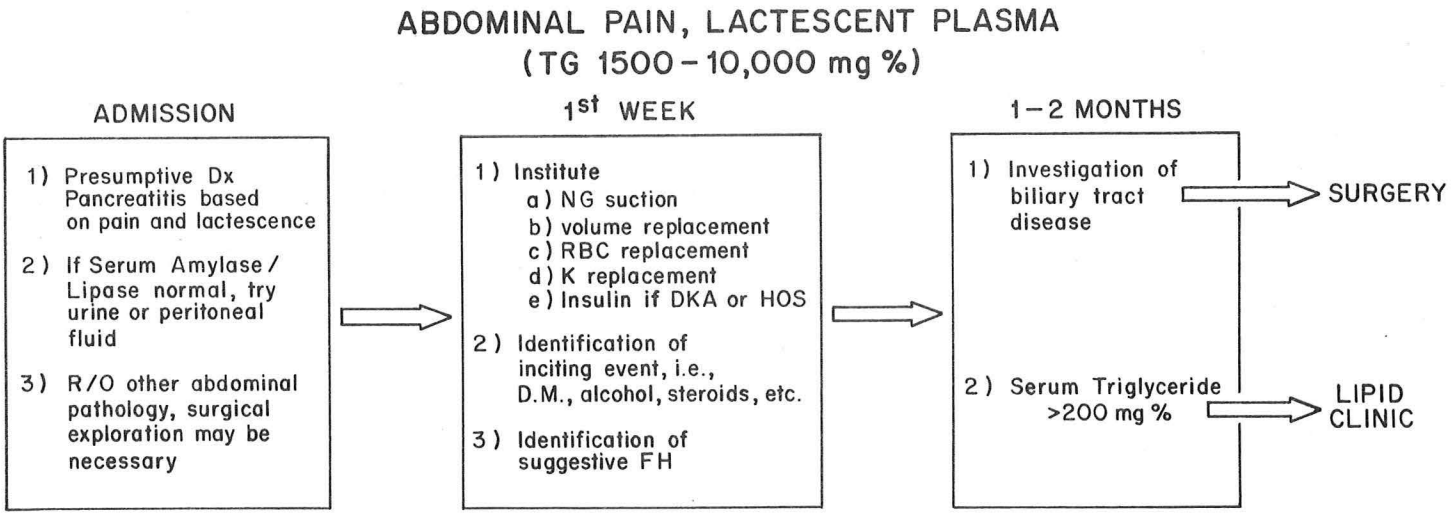
However, there are a number of diseases or exogenous materials that can significantly, but modestly, shift the distribution of these triglyceride levels to a slightly higher level. Thus, as shown by the dashed line, the

regular ingestion of alcohol, the administration of drugs such as estrogens, pregnancy, insulin deficiency and a number of other events are associated with slight to modest increases in the fasting triglyceride levels in a number of patients (see bibliography). As shown in the right panel (solid line) in patients who have one of the inherited familial disorders of triglyceride metabolism (familial hypertriglyceridemia, familial mixed hyperlipidemia, unclassified hyperlipidemia) the fasting serum triglyceride values manifest a significant but modest increase so that the fasting level is almost always greater than 200 mg/dl. Apparently, however, if such patients begin to drink excessively, become pregnant, take estrogen-containing drugs or also develop insulin deficiency then there may be a very marked shift in the triglyceride levels to the right with the development of triglyceride levels well in excess of 1500 mg%. It is this group, then, that seems to be at risk with respect to the development of pancreatitis. There are 2 other groups of patients where these relationships are less clear. First, it is uncertain whether inciting events such as alcohol intake, estrogens, etc. can ever produce severe hypertriglyceridemia (>1500 mg%) in normal subjects. In those cases in the literature where this has been claimed there is usually inadequate familial studies to rule out the possibility of an underlying inherited triglyceride disorder. Second, it is unclear what percentage of patients with an underlying familial triglyceride disorder develop severe hypertriglyceridemia in the absence of the superimposition of one of these inciting events. This certainly does occur in the case of familial hyperchylomicronemia where the inciting event can be simply considered the intake of dietary lipid. Other cases, usually with a "type V" pattern, have also been described. The cause of these very high lipid levels and the relationship of these cases to the well defined familial syndromes is, at the moment, unclear.

IX. THE WORKUP OF PATIENTS WITH PANCREATITIS

With the recognition that serum lipids may be an important factor in the production of recurrent acute pancreatitis it now seems apparent that more vigorous evaluation of patients with this disorder should be undertaken. Generally, when first seen in the hospital or emergency room patients may present with 1 of 3 separate syndromes. The first of these is shown diagrammatically in Figure 21 and consists of a group of patients who

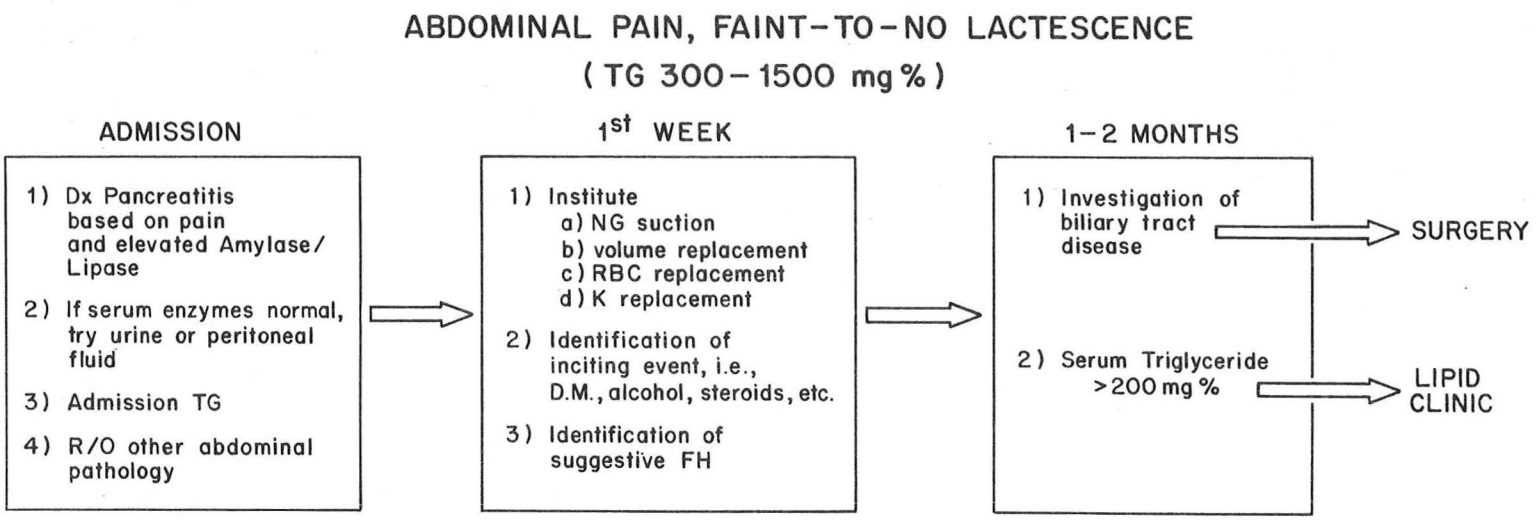
Figure 21



present with a grossly lactescent or creamy plasma and abdominal pain. Less commonly, these patients may present in shock from marked volume depletion or unconscious. The major point to be emphasized in this group is that the presumptive diagnosis of pancreatitis must be made from the combination of abdominal pain and a lactescent plasma since as many as 75% of these cases will have normal serum lipase or amylase values at the time they are first seen. Obviously, since the diagnosis of pancreatitis is a presumptive one in many of these subjects one must be extremely careful to rule out other major abdominal pathology such as a perforated peptic ulcer, acute cholecystitis or bowel infarction. Because of severe abdominal pain and a normal serum amylase many such patients reported in the literature have gone to surgical exploration where the diagnosis of pancreatitis was made. It is unclear from the literature why the severe hyperlipidemia interferes with determination of serum enzymes although at least 3 possible explanations have been suggested: 1) the presence of dialyzable inhibitors of enzyme reactions, 2) interference with the turbidometric methods by the chylomicrons or 3) binding of lipase and amylase to chylomicrons. In the absence of elevated serum enzymes when the patients are first seen, confirmation of the diagnosis of pancreatitis must be made by 1) serial dilutions of the serum in an attempt to overcome the inhibition in the enzyme assay, 2) the measurement of urinary amylase values and 3) measurement of enzyme levels in pleural or peritoneal fluid. None of these manipulations works in every case so that in a number of patients the diagnosis must be made on clinical grounds, or in a few cases, by surgical exploration. After admission, as also outlined in Figure 21, the usual therapy for acute pancreatitis should be instituted. This includes effective nasogastric suction which will have 2 major therapeutic effects: stimulation of the pancreas will be minimized and further synthesis of chylomicrons will be blocked. Other cardinal features of the treatment include volume replacement, potassium replacement and appropriate treatment of associated disorders such as diabetic ketoacidosis. During this initial period of workup the physician presumably will have identified the presence of inciting events such as diabetes, alcohol intake, oral contraceptives, etc., and will have obtained a preliminary family history that might indiciate an unusually high incidence of atherosclerotic complications suggesting an underlying familial disorder. Following recovery from the acute attack 2 major types of investigation should be carried out. First, each of these patients should have his biliary tract examined by appropriate Xray procedures. Patients with chronic cholecystitis and cholelithiasis should have cholecystectomy performed. Second, all of these patients also should have fasting serum triglyceride and cholesterol values run. Any subject having a fasting value > 200 mg% should be evaluated in the lipid clinic for the presence of an underlying lipid disorder. In the vast majority of these cases it is clear in the literature that effective treatment of the underlying lipid disorder with diet or drug manipulations and removal of inciting events (e.g. oral contraceptives, alcohol, etc.) will probably prevent future recurrent attacks of acute pancreatitis.

Figure 22 illustrates a second type of patients that may be seen with the syndrome of hypertriglyceridemia and abdominal pain. When this group of subjects is initially seen, however, they have serum which is essentially clear or has only mild lactescence even though they clearly have modest elevations of the triglyceride levels. This group of patients is presumably

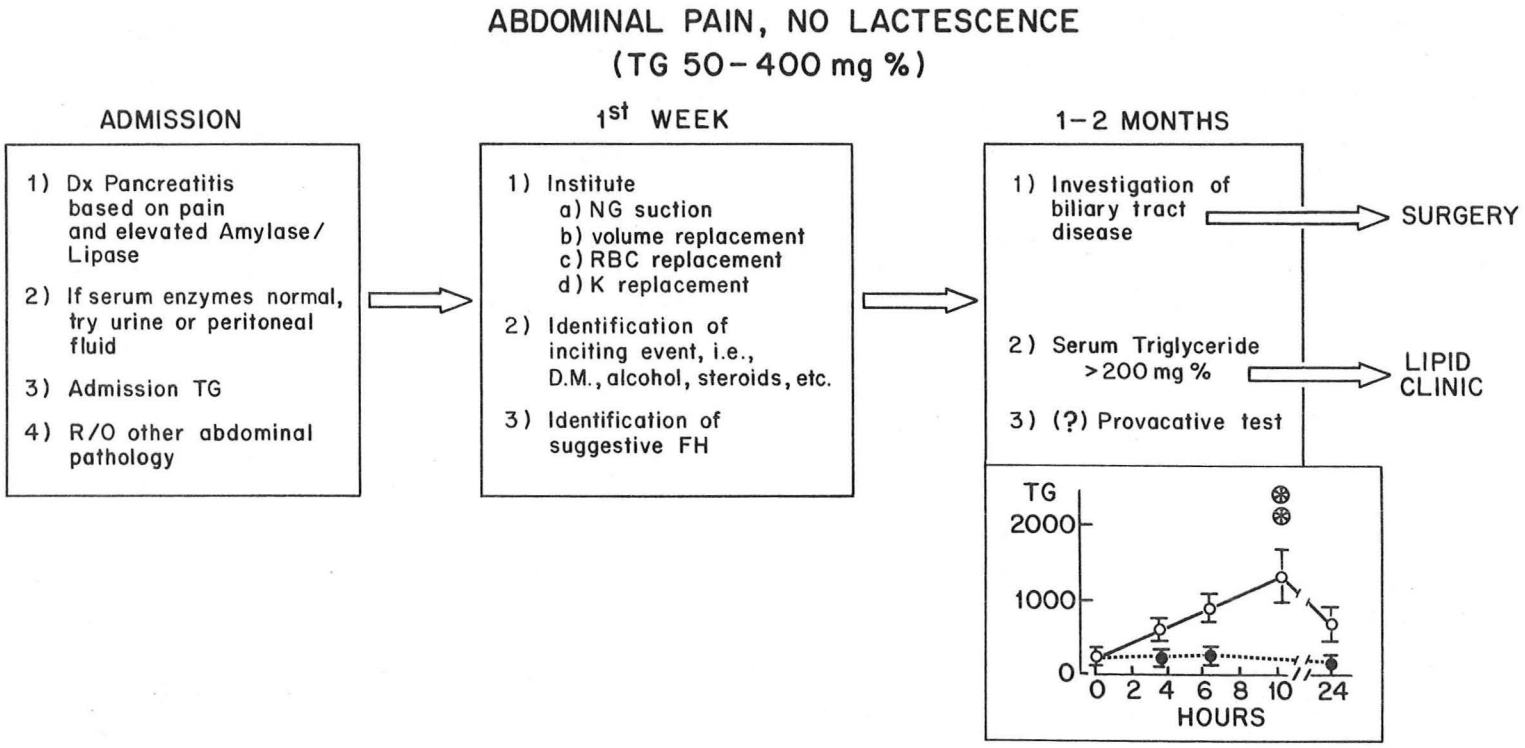
Figure 22



identical to those shown in Figure 21 except that there was a delay between the onset of acute pancreatitis and admission to the hospital. If, for example, the patient had the onset of abdominal pain, nausea and vomiting, stopped eating and finally came to hospital 1 to 3 days later then much of the hyperchylomicronemia may have cleared even though the pancreatitis was, in fact, induced by severe hypertriglyceridemia. In this group of patients serum lipase and amylase values may still be elevated or may have become elevated as the triglyceridemia diminished. There are a number of examples cited in the literature where serum amylase or lipase levels were normal initially when the plasma was very lactescent but these enzymes then became elevated over the subsequent 1-4 days as the hypertriglyceridemia cleared. This group of patients obviously should be treated and followed up as described for the preceding group of patients.

The final category includes those many patients seen in the emergency room or clinic who present with abdominal pain and clear plasma. In this group of patients investigation of the biliary tract and measurement of the fasting triglyceride levels is also indicated. Many of these subjects will have a history of excessive alcohol intake and, with lesser frequency, a history of some other inciting event. A number of these patients, however, will have no such history and will be found to have normal biliary tracts and fasting serum triglyceride levels of less than 200 mg%. There is a suggestion that even some patients in this group of "idiopathic" recurrent pancreatitis have a subtle and poorly defined abnormality in triglyceride metabolism. As shown by the right panel in Figure 23, when such patients are stressed by the administration of a very large amount of dietary triglyceride, some patients (solid line) develop an abnormally high postprandial hypertriglyceridemia and in one study 2 cases (indicated by asterisks) developed abdominal pain and pancreatitis in response to fat intake. Thus, it is of interest to

Figure 23



speculate that even in this group of patients with "idiopathic" pancreatitis there are unrecognized and subtle abnormalities in the handling of chylomicron triglyceride so that pancreatitis may be induced by the intake of a large lipid-rich meal. The importance of this possibility, however, remains to be elucidated.

REFERENCES

GENERAL FEATURES OF PANCREATITIS

1. Bilheimer, DW: Plasma lipid abnormalities associated with diabetes mellitus. Medical Grand Rounds. December 22, 1977.
2. Krejs, GJ: Pancreatic pseudocyst. Medical Grant Rounds. August 18, 1977.
3. Jamieson, JD: Anatomy of the Pancreas. In: The Science and Practice of Clinical Medicine, JP Sanford, editor. Vol. 1, p. 190, Grune & Stratton, New York, 1978.
4. Brandborg, LL: Acute pancreatitis. In: Gastrointestinal Disease, MH Sleisenger and JS Fordtran, editors. Chapter 92, p. 1158, WB Saunders, Philadelphia, 1973.

CHYLOMICRON AND LIPOPROTEIN METABOLISM

5. Zilversmit, DB: Chylomicrons. In: Structural and Functional Aspects of Lipoproteins in Living Systems, E Tria and AM Scanu, editors. Chapter C1, p. 329, Academic Press, New York, 1969.
6. Jackson, RL, JD Morrisett and AM Gotto: Lipoprotein structure and metabolism. Physiol Rev. 56:259, 1976.
7. Eisenberg, S: Lipoprotein metabolism and hyperlipemia. In: Atherosclerosis Reviews, R Paoletti and AM Gotto, editors. p. 23, Raven Press, New York, 1976.
8. Havel, RJ: Pathogenesis, differentiation and management of hypertriglyceridemia. Adv Intern Med. 15:117, 1973.
9. Bilheimer, DW: Hyperlipidemia. In: The Science and Practice of Clinical Medicine, JP Sanford, editor. Vol. 3, p. 464, Grune & Stratton, New York, 1978.
10. Fielding, CJ and RJ Havel: Lipoprotein lipase. Arch Pathol Lab Med. 101:225, 1977.

EXPERIMENTAL PANCREATITIS

11. Saharia, P, S Margolis, GD Zuidema and JL Cameron: Acute pancreatitis with hyperlipemia: studies with an isolated perfused canine pancreas. Surgery. 82:60, 1977.
12. Anderson, MC and JJ Bergan: Significance of vascular injury as a factor in the pathogenesis of pancreatitis. Ann Surg. 154:58, 1961.
13. Anderson, MC, WH Mehn and HL Method. An evaluation of the common channel as a factor in pancreatic or biliary disease. Ann Surg. 151:379, 1960.
14. Blumenberg, RM and SR Powers: Acute biliary pancreatitis: an experimental reappraisal of factors governing biliary reflux into the pancreas. Ann Surg. 158:1058, 1963.
15. Dardinski, VJ: Hemorrhagic pancreatitis. Report of two cases in which gallstones could not be considered essential etiological factors. Amer J Path. 7:169, 1931.
16. Dreiling, DA: Physiology of pancreatic secretion. Amer J Dig Dis. 4:581, 1959.

17. Lium, R and S Maddock: Etiology of acute pancreatitis: an experimental study. Surgery. 24:593, 1948.
18. McCutcheon, AD and D Race: Experimental pancreatitis: a possible etiology of postoperative pancreatitis. Ann Surg. 155:523, 1962.
19. Murray, MJ and AP Thal: The clinical significance of circulating pancreatic antibodies. Ann Intern Med. 53:548, 1960.
20. Parry, EW, GA Hallenbeck and JH Grindlay: Pressures in the pancreatic and common ducts; values after fasting, after various meals, and after sphincterotomy; an experimental study. AMA Arch Surg. 70:757, 1955.
21. Paulino-Netto, A and F Paulino: Pancreatic ductal reflux. Amer J Dig Dis. 8:666, 1963.
22. Walton, B, H Schapiro and ER Woodward: The effect of alcohol on pancreatic secretion. Surg Forum. 11:365, 1960.

ESTROGEN INDUCED HYPERLIPIDEMIA

23. Hazzard, WR, MJ Spiger, JD Bagdade and EL Bierman: Studies on the mechanism of increased plasma triglyceride levels induced by oral contraceptives. N Eng J Med. 280:471, 1969.
24. Glueck, CJ, D Scheel, J Fishback and P Steiner: Estrogen-induced pancreatitis in patients with previously covert familial type V hyperlipoproteinemia. Metabolism. 21:657, 1972.

ALCOHOL INDUCED HYPERLIPIDEMIA AND PANCREATITIS

25. Cameron, JL, DM Capuzzi, GD Zuidema and S Margolis: Acute pancreatitis with hyperlipemia. Amer J Med. 56:482, 1974.
26. Schapiro, H, LD Wruble and LG Britt: The possible mechanism of alcohol in the production of acute pancreatitis. Surgery. 60:1108, 1966.
27. Greenberger, NJ, FT Hatch, GD Drummey and KJ Isselbacher: Pancreatitis and hyperlipemia: a study of serum lipid alterations in 25 patients with acute pancreatitis. Medicine. 45:161, 1966.
28. Cameron, JL, GD Zuidema, and S Margolis: A pathogenesis for alcoholic pancreatitis. Surgery. 77:754, 1975.
29. Kudzma, DJ and G Schonfeld: Alcoholic hyperlipidemia: induction by alcohol but not by carbohydrate. J Lab Clin Med. 77:384, 1971.
30. Kessler, JI, JC Kniffen and HD Janowitz: Lipoprotein lipase inhibition in the hyperlipemia of acute alcoholic pancreatitis. N Eng J Med. 269:943, 1963.
31. Jaillard, J, P Dewailly, G Sezille, et al: Interet et signification du test d'hyperlipemie par voie veineuse dans l'exploration des hyperlipemies. Atherosclerosis. 19:493, 1974.
32. Braeman, J: Alcoholic hyperlipidemia. Lancet. p. 820, 1972.
33. Gavras, H, HR Brunner, ED Vaughan and JH Laragh: Alcohol-induced hyperlipidemia and beta lipoproteins. Science. 180:1372, 1973.
34. Ostrander, LD, DE Lamphiear, WD Block, et al: Relationship of serum lipid concentrations to alcohol consumption. Arch Intern Med. 134:451, 1974.
35. Chait, A, AW February, M Mancini and B Lewis: Clinical and metabolic study of alcoholic hyperlipidemia. Lancet. p. 62, 1972.
36. Barboriak, JJ: Hyperlipemia in alcoholics. Quart J Stud Alc. 35:15, 1974.

37. Jones, DP, MS Losowsky, CS Davidson and CS Lieber: Effects of ethanol on plasma lipids in man. J Lab Clin Med. 62:675, 1963.
38. Avogaro, P and G Cazzolato: Changes in the composition and physico-chemical characteristics of serum lipoproteins during ethanol-induced lipaemia in alcoholic subjects. Metabolism. 24:1231, 1975.
39. Isselbacher, KJ and NJ Breenberger: Metabolic effects of alcohol on the liver. N Eng J Med. 270:351, 1964.
40. Losowsky, MS, DP Jones, CS Davidson and CS Lieber: Studies of alcoholic hyperlipemia and its mechanism. Amer J Med. 35:794, 1963.
41. Ginsberg, H, J Olefsky, JW Farquhar and GM Reaven: Moderate ethanol ingestion and plasma triglyceride levels. Ann Intern Med. 80:143, 1974.

PANCREATITIS AND HYPERLIPIDEMIA IN DIABETES

42. Brunzell, JD, WR Hazzard, AG Motulsky and EL Bierman: Evidence for diabetes mellitus and genetic forms of hypertriglyceridemia as independent entities. Metabolism. 24:1115, 1975.
43. Steiner, G, M Poapst and JK Davidson: Production of chylomicron-like lipoproteins from endogenous lipid by the intestine and liver of diabetic dogs. Diabetes. 24:263, 1975.

PANCREATITIS IN HYPERLIPOPROTEINEMIA

44. Brunzell, JD and HG Schrott: The interaction of familial and secondary causes of hypertriglyceridemia: role in pancreatitis. In: Transactions of the Association of American Physicians. Atlantic City, NJ, Vol. 86, p. 245, 1973.
45. Greenberger, NJ: Pancreatitis and hyperlipemia. N Eng J Med. 289: 586, 1973.
46. Haig, THB: Experimental pancreatitis intensified by a high fat diet. Surg Gynecol Obstet. p. 914, November, 1970.
47. Wang, C, Adlersberg, D and EB Feldman: Serum lipids in acute pancreatitis. Gastroenterology. 36:832, 1959.
48. Klatskin, G and M Gordon: Relationship between relapsing pancreatitis and essential hyperlipemia. Amer J Med. p. 3, January, 1952.
49. Corazza, LJ and RM Myerson: Essential hyperlipemia. Amer J Med. p. 258, February, 1957.
50. Cameron, JL: Lipid Abnormalities and acute pancreatitis. Hospital Practice. p. 95, April, 1977.
51. Cameron, JL, C Crisler, S Margolis, TR DeMeester and GD Zuidema: Acute pancreatitis with hyperlipemia. Surgery. 70:53, 1971.
52. Cameron, JL, DM Capuzzi, GD Zuidema and S Margolis: Acute pancreatitis with hyperlipemia: the incidence of lipid abnormalities in acute pancreatitis. Ann Surg. 177:483, 1972.
53. Howard, JM, E Ehrlich, JJ Spitzer and LM Singh: Hyperlipemia in patients with acute pancreatitis. Ann Surg. 160:210, 1964.
54. Howorth, MB: Pancreatitis and hyperlipoproteinemia. South Med J. 66:1260, 1973.
55. Farmer, RG, EI Winkelman, HB Brown, LA Lewis: Hyperlipoproteinemia and pancreatitis. Amer J Med. 54:161, 1973.

56. Cross, DF: Recurrent pancreatitis and fat-induced hyperlipoproteinemia. JAMA. 208:1494, 1969.
57. Greenberg, BH, WC Blackwelder and RI Levy: Primary type V hyperlipoproteinemia. A descriptive study in 32 families. Ann Intern Med. 87:526, 1977.
58. Wang, C, L Strauss and D Adlersberg: Experimental pancreatitis and plasma lipids. Gastroenterology. 35:465, 1958.

FAMILIAL HYPERLIPOPROTEINEMIA

59. Goldstein, JL, WR Hazzard, HG Schrott, EL Bierman and AG Motulsky: Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. J Clin Invest. 52:1533, 1973.
60. Goldstein, JL, HG Schrott, WR Hazzard, EL Bierman and AG Motulsky: Hyperlipidemia in coronary heart disease. II. Genetic analysis of lipid levels in 176 families and delineation of a new inherited disorder, combined hyperlipidemia. J Clin Invest. 52:1544, 1973.
61. Hazzard, WR, JL Goldstein, HG Schrott, AG Motulsky and EL Bierman: Hyperlipidemia in coronary heart disease. III. Evaluation of lipoprotein phenotypes of 156 genetically defined survivors of myocardial infarction. J Clin Invest. 52:1569, 1973.

AMYLASE DETERMINATIONS IN HYPERLIPEMIA AND WITH VARIOUS DISORDERS

62. Berk, JE and L Bridhandler: Advances in the interpretation of hyperamylasemia. In: Progress in Gastroenterology, Vol. III, GBJ Glass, editor. Grune & Stratton, New York, 1977.
63. Gitlitz, PH and CS Frings: Interferences with the starch-iodine assay for serum amylase activity, and effects of hyperlipemia. Clin Chem. 22:2006, 1976.
64. Fallat, RW, JW Vester and CJ Glueck: Suppression of amylase activity by hypertriglyceridemia. JAMA. 225:1331, 1973.
65. Warshaw, AL and PB Lesser: Amylase clearance in differentiating acute pancreatitis from peptic ulcer with hyperamylasemia. Ann Surg. 181: 314, 1975.
66. Myhre, J, S Nesbitt and JT Hurly: Response of serum amylase and lipase to pancreatic stimulation as a test of pancreatic function. Gastroenterology. 13:127, 1949.
67. Muether, RO and WA Knight: Chronic recurrent pancreatitis. I. Clinical and laboratory aspects. Gastroenterology. 12:24, 1949.
68. Burton, P, EM Hammond, AA Harper, et al: Serum amylase and serum lipase levels in man after administration of secretin and pancreozymin. Gut. 1:125, 1960.