PULMONARY COMPLICATIONS OF HEPATIC AND PANCREATIC DISEASE

Parkland Memorial Hospital Grand Rounds
May 24, 1979

K. Joy Robertson, M.D.

University of Texas Health Science Center
Dallas, Texas

PULMONARY COMPLICATIONS OF HEPATIC AND PANCREATIC DISEASE

Introduction

I. PULMONARY COMPLICATIONS OF HEPATIC DISEASE

- A. Hypoxemia
- B. Hyperventilation
- C. Pleural Effusions
  1. Hepatic Hydrothorax
  2. Chylothorax
  3. Subdiaphragmatic Infections
     - a. Hepatic Amebiasis
     - b. Pyogenic Abscess of Liver
     - c. Hepatitis with B Antigen
     - d. Spontaneous Bacterial Empyema
     - e. Miscellaneous Causes
- D. Hepatic Disease with Adult Respiratory Distress Syndrome
  1. Incidence
  2. Hemodynamic Changes
  3. Syndrome and Prognosis
  4. Predisposing Factors
- E. Fibrosing Alveolitis and Chronic Liver Disease

II. PULMONARY COMPLICATIONS OF PANCREATIC DISEASE

- A. Incidence
- B. Pleural Effusions
  1. Incidence and Characteristics
  2. Differential Diagnosis
  3. Theories of Etiology
  4. Treatment
- C. Pancreatitis with ARDS
  1. Incidence
  2. Clinical Syndrome
  3. Physiological Abnormalities
  4. Pathogenesis of Pulmonary Edema
  5. Treatment

Summary

INTRODUCTION

The incidence, severity and therapeutic implications of the pulmonary complications of hepatic and pancreatic disease warrant greater attention than has been afforded them in the internal medicine literature. Although the hypoxemia and hyperventilation of chronic liver disease are well reported, the diverse etiologies of pleural effusions, the frequency of the adult respiratory distress syndrome and the association of fibrosing alveolitis with liver disease are less well appreciated. Likewise, the thoracic complications of pancreatitis are not well reviewed even though such have been reported in up to 80 percent of patients (1) and may be a contributing cause of death in up to 39 percent of fatalities (2). This review will indicate the magnitude of the pulmonary problems associated with hepatic and pancreatic diseases and will review the diagnostic and therapeutic armamentarium currently available.

I. PULMONARY COMPLICATIONS OF HEPATIC DISEASE

A. Hypoxemia

The phenomena of clubbed fingers and cyanosis in the absence of cardiopulmonary disease was first described in patients with hepatic disease in 1884 by Fluckiger (3), although the accompanying hyperventilation was not appreciated until the late 1950's (4). Actual measurements of arterial oxygen desaturation were first reported in 1935 (5). Occasional reports of patients with severe hypoxemia in association with clubbing and spider nevi have appeared, but such patients are exceptional. Rodman's study of 56 patients with Laënnec's cirrhosis and without cardiopulmonary disease indicates that hypoxemia is usually moderate; the distribution of values he reported are presented in Table 1 (6).

TABLE 1

ARTERIAL OXYGEN SATURATION IN PATIENTS WITH LAËNNEC'S CIRRHOSIS

Saturation Percent	Number of Patients	Percent of Group
> 94	7	12
92 - 93.9	20	36
90 - 91.9	20	36
85 - 89.9	8	14
< 85	1	2
TOTAL	56	100

The mean arterial hemoglobin oxygen saturation was 92 percent. Eighty-seven percent of patients demonstrated hypoxemia, but only 16 percent could be regarded as severe, and only one patient had exceptionally marked hypoxemia. Other studies demonstrate similar variation in the presence and degree of hypoxemia (5, 17). However, none have found a correlation with the severity of liver disease as assessed by liver function studies or with hepatic encephalopathy, Table 2 (7).

TABLE 2

ARTERIAL OXYGEN SATURATION AND LEVEL OF CONSCIOUSNESS
(n = 23)

Coma Grade	Percent Saturation
0	93
1 - 2	91
3 - 4	91

(p = N.S.)

Four causes of the hypoxemia of chronic liver disease have been suggested, Table 3.

TABLE 3

CAUSES OF ARTERIAL DESATURATION IN CHRONIC LIVER DISEASE

1) Decreased oxygen affinity of hemoglobin (8)
2) Porto-pulmonary shunts (9, 10-12)
3) Arterio-venous shunts (6, 13-15)
4) Ventilation-perfusion imbalance (16, 17)

A decreased arterial oxygen saturation as a result of a decrease in the affinity of hemoglobin for oxygen (a shift of the oxyhemoglobin desaturation curve to the right) was reported in 1938. However, such could not result in arterial hypoxemia in the absence of lung disease. Additionally, this finding has not been reproduced by all investigators.

Anatomic porto-pulmonary anastomoses have been demonstrated and quantitated by several investigators. However, there is substantial evidence that they are not the major contributor to venous admixture. First, the hypoxemia frequently persists at similar levels after successful porto-systemic shunt. Further, portal blood has a relatively high oxygen saturation, and hence the shunt would have to be of great magnitude to account for severe hypoxemia (18). However, since these channels do exist, it is reasonable to conclude that they may contribute to arterial desaturation.

Pulmonary arterio-venous communications have been demonstrated in cirrhotics by post-mortem injections (13, 14), and their existence has been verified in life by cardiac catherization and pulmonary function data (12, 19). These anastomoses have occasionally also been visualized by pulmonary angiography in patients with liver disease (20). Pulmonary shunts are likely the most important cause of hypoxemia, but their anatomical site in the lung is uncertain. Possibilities include blood shunted through atelectatic areas, newly formed arterio-venous connections, and the opening of previously nonfunctioning precapillary communications under the influence of a vasoactive substance (21-24). Recent evidence by Robin, et. al., (25) supports the contention that pulmonary right to left shunting accounts for the hypoxemia in severely desaturated patients, Table 4.

TABLE 4

BASAL VASCULAR SHUNTS IN CIRRHOSIS

	Lying	Sitting
P_aO_2 mm Hg	56	40
Q_s/Q_t	20	42
Angiogram	+	+
Lung scan	+	+

These data were from three patients with severe liver disease who were platypnic and orthodeoxic. [Platypnea refers to severe dyspnea on assuming a sitting position that is relieved by lying down. Orthodeoxia refers to a reduction in arterial oxygen saturation on sitting that is relieved by lying down]. Each patient had a normal TLC, FVC, and $FEV_{1.0}$ and each had intrapulmonary shunts that were demonstrable by lung scan and angiography. On assuming an erect position both blood flow to the bases and the right to left shunt increased, the latter on average 20 percent.

Finally, in regard to hypoxemia, there is increasing evidence that regional lung function is altered in non-ascitic cirrhotic patients, Table 5 (16).

TABLE 5

REGIONAL LUNG FUNCTION IN PATIENTS
WITH HEPATIC CIRRHOSIS
(n = 11)

Regional RV (Bases) 50% > normal

Closing Volume > FRC

Ruff, et. al., studied 11 mildly hypoxemic, non-ascitic cirrhotic patients with normal lung volumes and spirometry. He found that all had increased residual volumes at the bases of the lung and that the closing volumes were always greater than functional residual capacity. These abnormalities indicate gas trapping and subsequent ventilation-perfusion imbalance. A mild degree of hypoxemia could be explained by the magnitude of the ventilation perfusion abnormality.

B. Hyperventilation

Hyperventilation is commonly encountered in all types of chronic liver disease. The incidence of this finding from four series which include patients with varying severity of liver disease is given in Table 6 (7, 26-28).

TABLE 6

INCIDENCE OF HYPOCAPNIA IN PATIENTS WITH HEPATIC DISEASE

Total Patients	P_aCO_2<36 (mm Hg)	Percent
63	37	58

In contrast to hypoxemia, hypocapnia is significantly related to the anatomic severity of liver disease and to the presence and level of hepatic coma, Table 7 (7).

TABLE 7

ARTERIAL CARBON DIOXIDE TENSION AND LEVEL OF CONSCIOUSNESS (n = 23)

Coma Grade	P_aCO_2 mm Hg
0	37.5
1 - 2	33.3
3 - 4	31.8

(p = <0.01)

The stimulus for hyperventilation remains conjectural. The most popular theories are listed in Table 8 (28).

TABLE 8

POTENTIAL CAUSES OF HYPOCAPNIA IN CHRONIC LIVER DISEASE

1) Arterial desaturation
2) Progesterone
3) Ammonia
4) Increased responsiveness to carbon dioxide
5) Vasoactive intestinal polypeptide

Arterial desaturation is not likely to be the stimulus for hyperventilation. There is no correlation between the level of hypoxemia and hyperventilation, and the administration of oxygen does not ablate the hypocapnia (26). Further, the arterial oxygen tension that is usually observed is well above the threshold for respiratory center stimulation, approximately 65 mm Hg (29).

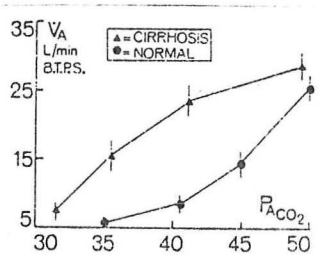
Progesterone, which is dependent on the liver for its breakdown, has been shown to be a ventilatory stimulant when administered to patients in respiratory failure (30, 31) and an elevated blood concentration is thought to be responsible for the hyperventilation of pregnancy (32, 33). It has been suggested that progesterone may be the stimulus for hyperventilation in cirrhotic patients. However, plasma levels are not significantly elevated above normal in persons with liver disease (34).

Ventilatory stimulation by ammonia or its metabolites has often been suggested as the cause of the hyperventilation. Blood levels may be increased due to decreased metabolic capacity of the liver and due to shunting of portal blood. Blood levels of ammonia have been correlated with the degree of hyperventilation by some (35) but not by other investigators (27). This lack of consistency is difficult to explain if ammonia is the only etiology of the hyperventilation.

In 1967 Karetzy, et. al., reported on seven cirrhotic patients without evidence of pulmonary disease who had an augmented ventilatory response to arterial carbon dioxide tension in the range of 30-40 mm Hg, Figure 1 (28).

FIGURE 1

VENTILATORY RESPONSE TO CARBON DIOXIDE IN NORMAL AND CIRRHOTIC SUBJECTS



These investigators also demonstrated that cellular buffering mechanisms were intact and concluded that the increased respiratory center responsiveness may be mediated by ammonia (36) or an intracellular acidosis of the respiratory center. They presented no direct evidence in this regard.

It has recently been reported that plasma levels of vasoactive intestinal polypeptide (VIP) are increased in some but not all cirrhotic patients. VIP has been demonstrated to be a direct respiratory stimulant. However, the inconsistency of elevation of blood levels argues against VIP being the sole cause (37).

From this review it appears that the cause of hyperventilation in patients with liver disease remains unknown and may be multifactorial.

C. Pleural Effusion

1. Hepatic Hydrothorax

An association of hydrothorax with cirrhosis has been recognized since 1927 (38). The reported incidence ranges from 0.4 percent to 10 percent of all cirrhotic patients (39, 40). The distribution of these effusions, which are almost exclusively transudates, is given in Table 9 (41).

TABLE 9

DISTRIBUTION OF HEPATIC HYDROTHORAX

Location	Percent
Right	67
Left	17
Bilateral	17

Right sided effusions are much more common than left sided or bilateral effusions. The pleural fluid is similar in character to the ascitic fluid although the protein, cholesterol and total lipids may be higher in pleural than peritoneal fluid. The source of chest fluid found in association with cirrhosis is unknown. Proposed mechanisms are given in Table 10.

TABLE 10

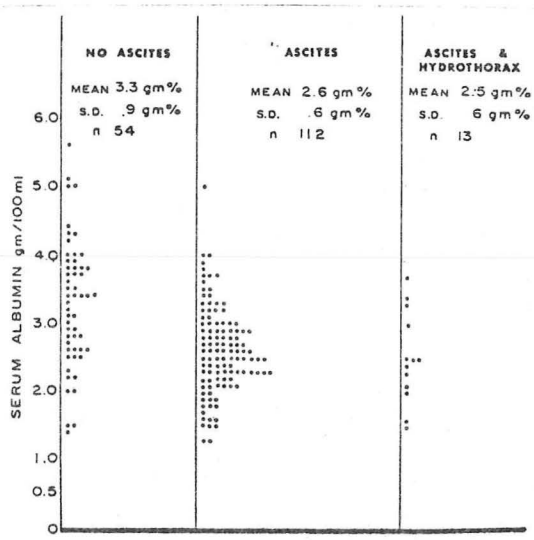
MECHANISM OF PRODUCTION PLEURAL FLUID IN CIRRHOSIS

1) Hypoalbuminemia
2) Azygous hypertension
3) Direct passage thru diaphragm
4) Passage thru diaphragmatic lymphatics

Hypoalbuminemia as the sole cause of pleural fluid has been investigated, and the results are presented in Figure 2 (41).

FIGURE 2

SERUM ALBUMIN LEVELS IN 179 CASES OF CIRRHOSIS

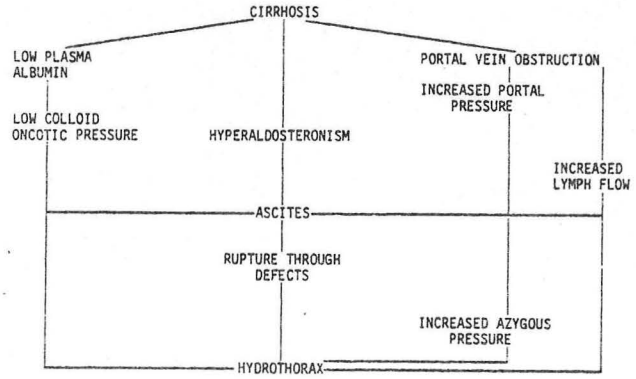


There is a tendency for patients with ascites to have lower serum albumin concentrations than patients without ascites. However, there is no difference between patients with ascites who do or do not also have hydrothorax.

Azygous hypertension secondary to portal hypertension has been documented (42), and various investigators have demonstrated diaphragmatic defects, especially on the right side (41). There is also good evidence for augmented transdiaphragmatic lymph flow (41). Thus, it is reasonable to assume that hepatic hydrothorax has a multifactorial etiology. The schema presented in Figure 3 combines all four mechanisms and may well be operative is the usual case of hepatic hydrothorax with ascites.

FIGURE 3

MECHANISMS FOR PRODUCTION OF HEPATIC HYDROTHORAX



Although occasional patients have been reported with hepatic hydrothorax without ascites (43), in most cases the pleural fluid can be considered an extension of the peritoneal fluid. For this reason the initial treatment is always directed at treatment of ascites. When successful, the pleural fluid usually resolves spontaneously. In more refractory patients with dyspnea and a large amount of pleural fluid, thoracentesis may be required for symptomatic relief. In this situation the fluid tends to reaccumulate and thoracentesis may result in further protein depletion. Recent reports indicate that instillation of tetracycline in the pleural space by tube thoracostomy may induce pleural symphysis and successfully prevent recurrence of hydrothorax (44). However, experience with malignant pleural effusions argues against success in all cases of refractory hydrothorax (45).

2. Chylothorax

Chylothorax without chylous ascites was first reported in 1965 as a rare complication of chronic liver disease (46). A potential pathogenesis of chylothorax is listed in Table 11.

TABLE 11

LYMPHATICS IN CHRONIC LIVER DISEASE

1) Increased flow in thoracic duct
2) Increased pressure in thoracic duct
3) Rupture of thoracic duct

Increased flow leading to increased pressure have been recorded in liver lymphatics and the thoracic duct in chronic liver disease (47, 48). Rupture of lymphatic channels is therefore postulated as the etiology of chylous effusion in this situation. Spontaneous remissions of chylous effusions are frequently observed, lending support to this theory. The treatment of chylous effusion is tube thoracostomy as needed for relief of dyspnea.

3. Subdiaphragmatic Infections

a. Hepatic Amebiasis

Hepatic abscess is the most common complication of amebiasis followed by pleuropulmonary involvement. The incidence of pleuropulmonary complications ranges from .01 percent to 16 percent of all documented cases (51). Pulmonary amebiasis is usually secondary to hepatic involvement; however, hematogenous spread from intestinal sources has been reported (49). When pleuropulmonary amebiasis is secondary to hepatic abscess, there may be direct spread through the diaphragm, transdiaphragmatic lymphatic extension, or hematogenous spread, but 75 percent of cases occur by direct extension (50). The mode of spread has both therapeutic and prognostic implications.

The manifestations of pleuropulmonary amebiasis, based on 20 cases, are listed in Table 12 (49, 51).

TABLE 12

MANIFESTATIONS OF PLEUROPULMONARY DISEASE
SECONDARY TO HEPATIC AMEBIASIS

1) Diaphragmatic elevation
2) Sympathetic effusion
3) Pulmonary infiltrates or abscess
4) Amebic empyema
5) Broncho-hepatic fistula

Diaphragmatic elevation is the most common abnormality. It is non-specific and does not imply invasion of the thorax by ameba. The specific incidence of sympathetic effusion is not reported but evidently is not frequent. Pulmonary infiltrates or abscesses without effusion may occur either by hematogenous spread or direct extension. Amebic empyema and broncho-hepatic fistula occur only with direct extension.

The mortality of untreated pulmonary amebiasis is given in Table 13 and relates to type of involvement (52).

TABLE 13

MORTALITY OF UNTREATED
PULMONARY AMEBIASIS
(n = 153)

Type of Involvement	Percent Mortality
Empyema	78
Empyema with lung abscess	42
Broncho-hepatic fistula	10

Metronidazole has revolutionized the treatment of hepatic amebiasis, and drainage is not always necessary. Moreover, therapy with metronidazole has reduced the mortality of hepatic or pleuropulmonary amebiasis to a small fraction of patients. However, a report of 10 cases of pleuropulmonary disease that did not respond to metronidazole alone reaffirms that mechanical problems may still necessitate thoracotomy. These complications are listed in Table 14 (51).

TABLE 14

COMPLICATIONS OF MEDICALLY TREATED
PULMONARY AMEBIASIS
(n = 10)

Involvement	Complication Requiring Thoracotomy
Empyema	Trapped lung requiring decortication
Lung abscess	Adherent diaphragm with communication to lung
Hepatobronchial fistula	Middle lobe atelectasis secondary to diaphragmatic adhesions

In each case despite two weeks of medical treatment coupled with repeat thoracentesis extensive pleural reaction required some decortication or lobectomy. This experience supports surgical treatment to prevent pulmonary dysfunction in patients with empyema. In lung abscess alone endobronchial drainage may be established and surgery may be averted.

b. Pyogenic Abscess of Liver

Pyogenic abscess of the liver is most frequently associated with ascending cholangitis, but the source may be ubiquitous, and still unidentified after laparotomy (52). Pulmonary manifestations are estimated to occur in approximately 50 percent of cases, Table 15 (52, 53).

TABLE 15

INCIDENCE AND TYPE OF PULMONARY MANIFESTATIONS
OF PYOGENIC LIVER ABSCESS
(n = 106)

	Number of Patients	Percent
Normal Chest X-ray	54	51
Abnormal Chest X-ray		
Elevated hemidiaphragm alone	17	16
Atelectasis with infiltrate	16	15
Pleural effusion	20	19

Since hepatic abscesses may be single or multiple, either hemidiaphragm may be elevated and atelectasis or effusions can occur in either hemithorax. The effusions are exudative in character and are

otherwise non-specific. Empyema is relatively uncommon. Treatment of these pulmonary complications is limited to the antimicrobial and surgical treatment of the primary disease (53).

c. Hepatitis with B Antigen

Pleural effusions have been reported in a few patients with hepatitis; the diagnosis was made by exclusion of other causes (54, 55). However, in a recent report of bilateral pleural effusions associated with clinical hepatitis, hepatitis B antigen and hepatitis B surface antigen were demonstrated (56). The antigen titers were similar to serum, and virus particles were seen on electron microscopy of the pleural fluid. Autopsy ruled out other causes of the pleural effusion. Insufficient reports are available to estimate the incidence or character of hepatitis associated effusions. However its presence and probable infectivity to medical personnel is established (56). The best therapy of the effusion is not known. However, if it is suspected that the fluid is secondary to hepatitis B, relief of dyspnea is likely the only indication of further intervention.

d. Spontaneous Bacterial Empyema

Spontaneous bacterial peritonitis is a well described entity; the source of the bacteria is frequently unknown. Empyema secondary to *E. coli* has been described in the absence of pneumonia (57, 58). It apparently occurs only in patients with chronic ascitic pleural effusions. Although ascitic fluid may be sterile, it has been suggested that the empyema is secondary to a less virulent peritonitis which enters the chest by previously described communications. Treatment includes tube thoracostomy as well as antimicrobials.

e. Miscellaneous Causes

Pleural effusions have been reported with infected hydatid cysts of the liver and following an infected liver biopsy. The manifestations are similar to pyogenic liver abscess.

D. Hepatic Disease with Adult Respiratory Distress Syndrome

Regardless of etiology, the adult respiratory distress syndrome is best characterized as non-cardiogenic pulmonary edema. Lung injury results in excessive pulmonary capillary permeability and fluid leakage into the extravascular interstitium and alveoli despite normal left atrial pressures.

1. Incidence

The adult respiratory distress syndrome has only recently been recognized as a complication of hepatic decompensation and hence the incidence has not been quantitated. The best estimate is from a single series of patients with diverse etiologies of hepatic failure, Table 16 (59).

TABLE 16

INCIDENCE OF NON-CARDIOGENIC PULMONARY EDEMA
IN GRADE IV HEPATIC COMA
(n = 100)

Etiology of Hepatic Failure	Number of Patients	Number with Pulmonary Edema
Acute Viral Hepatitis		
B Ag. neg.	31	8 (26%)
B Ag. pos.	13	6 (46%)
Paracetamol overdose	37	15 (44%)
Halothane associated	9	4 (44%)
Miscellaneous	10	4 (40%)
TOTAL	100	37 (37%)

The very high incidence of 37 percent in this series is probably attributable to obtaining routine daily chest radiograms. Although acute viral hepatitis, parecetamol overdose and halothane associated hepatitis are very acute hepatic insults, other authors have reported the same phenomena in the more subacute forms of liver decompensation due to Laënnec's cirrhosis and acute alcoholic liver disease. Patients with either acute or chronic alcoholic liver disease were less encephalopathic at the onset of respiratory distress than patients with liver disease due to other etiologies (60).

2. Hemodynamic Changes

Hemodynamic parameters in patients with and without pulmonary edema indicate that the pulmonary edema associated with liver disease is non-cardiogenic, Table 17 (59).

TABLE 17

HEMODYNAMIC DATA IN PATIENTS WITH HEPATIC FAILURE
WHO DO AND DO NOT HAVE PULMONARY EDEMA

	Pulmonary Edema	No Pulmonary Edema
Pulmonary Capillary Wedge Pressure	6.3 mm Hg	4.8 mm Hg
Cardiac Output	7.5 l/min	6.8 l/min
Positive Fluid Balance	820 ± 37 ml	787 ± 43 ml
Shunt Fraction	42.0 ± 4%	25.3 ± 1.3%
Pulmonary Extravascular Water	568 ± 114 ml	108 ± 18 ml

The pulmonary capillary wedge pressure and cardiac output were within the normal range in both groups of patients, and the positive fluid balance was not statistically different. The percent of the cardiac output shunted was statistically increased in the pulmonary edema group and correlated with the amount of extravascular water.

3. Syndrome and Prognosis

The ARDS syndrome of progressive respiratory distress, refractory hypoxemia and diffuse bilateral alveolar infiltrates usually occurs in patients whose liver damage is severe. It has been correlated with increasing depth of coma and with prolongation of the prothrombin time. Onset is from one to nine days ($\bar{x}$ 4) after the onset of coma (59). Patients are initially hypocapnic, but ventilator support is usually necessary due to increasing tissue hypoxia. As in other etiologies of the ARDS syndrome, the mortality is high, probably in excess of 80 percent regardless of therapy, Table 18 (59, 60).

TABLE 18

ARDS AND HEPATIC FAILURE

Number of Patients	Mortality	Percent
45	37	82

The prothrombin time correlates with mortality being the least prolonged in those patients who survive (59).

4. Predisposing Factors

Patients with chronic liver disease, particularly those with hepatic failure, have several factors that predispose them to the development of non-cardiogenic pulmonary edema, Table 19.

TABLE 19

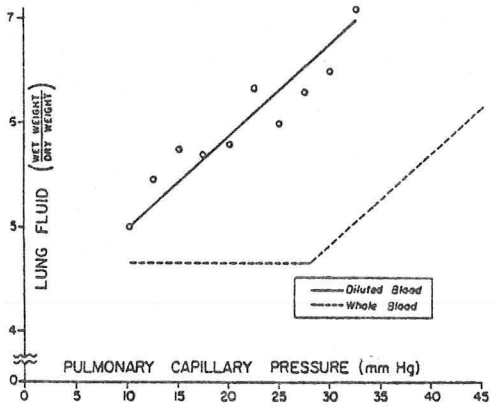
FACTORS PREDISPOSING TO PULMONARY EDEMA IN HEPATIC DISEASE

1) Hypoalbuminemia (Decreased Colloid Oncotic Pressure)
2) Cerebral Edema
3) Disseminated Intravascular Coagulation
4) Sepsis
5) Hypotension

Hypoalbuminemia results in a lowering of the plasma colloid oncotic pressure.

FIGURE 4

EFFECT OF COLLOID ONCOTIC PRESSURE AND
CAPILLARY PRESSURE ON LUNG WATER

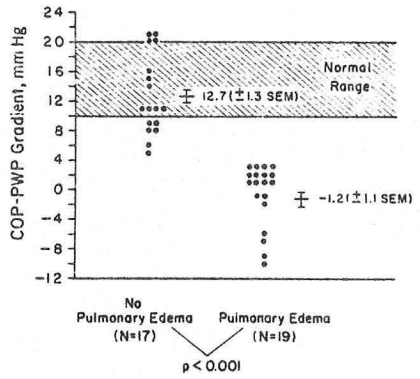


The data in Figure 4 show that lung fluid increases more rapidly for any increase in pulmonary capillary pressure if the colloid oncotic pressure is decreased. This finding indicates that the rate of fluid transudation is not a function of capillary pressure alone, but of capillary pressure minus the colloid oncotic pressure of blood in accord with the Starling hypothesis (61).

Although most patients with chronically decreased oncotic pressures do not develop pulmonary edema, there is a correlation between a low colloid oncotic pressure - pulmonary artery wedge pressure gradient (COP-PWP) and the development of non-cardiogenic pulmonary edema in the seriously ill. In a study of 128 patients who were critically ill with conditions of diverse etiology Rackow found the correlation between COP-PWP gradient and pulmonary edema which is presented in Figure 5 (62).

FIGURE 5

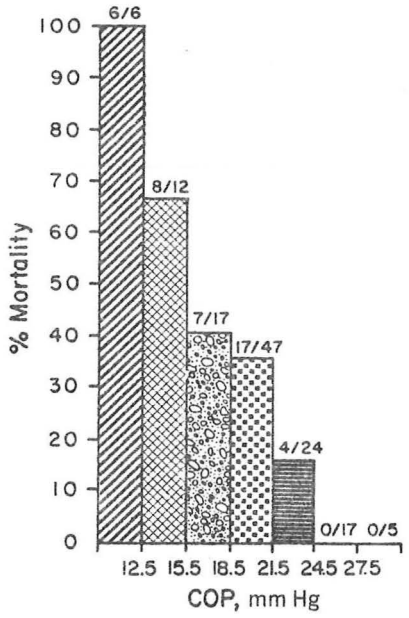
CORRELATION OF COP-PWP GRADIENT
AND PULMONARY EDEMA



He found that all patients with a COP-PWP gradient of < 4 mm Hg developed pulmonary edema. The non-cardiogenic pulmonary edema patients had normal wedge pressures but colloid oncotic pressures significantly lower than those with cardiogenic pulmonary edema. He was also able to correlate mortality with colloid oncotic pressure, Figure 6.

FIGURE 6

COLLOID ONCOTIC PRESSURE VERSUS MORTALITY



All patients with a COP of 12.5 mm Hg or less expired, while all patients with a COP greater than 24.5 mm Hg survived. The observed 50 percent survival was a pressure of 16.0 mm Hg. COP was a reliable predictor of survival 75 percent of the time ($p<0.001$). From his data it can be concluded that the COP-PWP gradient in seriously ill patients is useful in predicting pulmonary edema and that colloid oncotic pressure alone is a reliable prognostic index of mortality.

Many patients with liver disease have a bleeding tendency secondary to platelet abnormalities, deficiencies of clotting factors, increased fibrinolytic activity, and diffuse intravascular coagulation. There is both clinical and experimental evidence that diffuse intravascular coagulation may be important in producing the adult respiratory distress syndrome (63). Although the role of DIC in this regard has not been carefully delineated it is reasonable to assume that if DIC is present it may contribute to lung injury.

Patients in hepatic coma are at increased risk of developing sepsis (64). Regardless of whether the primary site of infection is the lung, spontaneous bacterial peritonitis, or some other source, the offending organisms are frequently gram negative bacilli. Non-cardiogenic pulmonary

edema is highly associated with gram negative bacillary sepsis and may also occur with sepsis of other etiologies (65). Sepsis results directly in pulmonary capillary-endothelial damage and additionally may induce DIC which may cause additional damage (66).

Patients in hepatic coma have a tendency to blood loss with resulting hypotension due to gastrointestinal bleeding. Whether hypotension alone results in non-cardiogenic pulmonary edema is still controversial. However, it is known that crystalloid therapy for shock results in pulmonary edema at low wedge pressures due to the low colloid oncotic pressure as previously discussed (61). Thus, the treatment of the bleeding that leads to hypotension may be a predisposing factor to the development of this syndrome.

Non-cardiogenic pulmonary edema may occur as a result of a variety of acute cerebral lesions. Hepatic coma reflects severe derangement of brain function and may be associated with elevated intracranial pressure, cerebral edema, and seizure disorders (59, 67). It may be that this cerebral dysfunction results in the massive sympathetic discharge necessary to produce neurogenic pulmonary edema; this possibility has not been addressed.

The treatment of the adult respiratory distress syndrome in the setting of hepatic failure is beyond the scope of this review. Such treatment employs non-specific support frequently including continuous artificial ventilation. Reversal of the hepatic decompensation is probably the most important determinant of outcome. Dexamethasone, 16 mgm per day, administered to 34 patients could not be demonstrated to benefit any parameter studied (59).

E. Fibrosing Alveolitis and Chronic Liver Disease

The term fibrosis alveolitis was introduced by Scadding in England to indicate the syndrome that is labeled chronic idiopathic interstitial fibrosis or chronic Hamman-Rich syndrome in this country (68). In 1968 Turner-Warwick reported eight patients with concomitant fibrosing alveolitis, chronic liver disease, autoantibodies and circulating immunoglobulins (69). Other investigators have failed to demonstrate either an increased incidence of interstitial lung disease in patients with liver disease (70) or an increased incidence of liver disease in patients with interstitial pulmonary fibrosis (71). It seems likely that the patients she described had systemic disease that fortuitously involved both lung and liver. Chronic liver disease should not be considered a predisposing factor to interstitial pulmonary fibrosis.

II. PULMONARY COMPLICATIONS OF PANCREATIC DISEASE

A. Incidence

Thoracic complications of pancreatitis occur frequently, and the potential severity is often underestimated. When present, such

complications are associated with a high morbidity, and mortality rates range from 5 (72) to 48 percent (73). The cause of death in 370 patients who died with pancreatitis emphasizes the importance of respiratory complications (74), Table 20.

TABLE 20

CAUSES OF DEATH IN 370 PATIENTS WITH PANCREATITIS

Adult Respiratory Distress Syndrome	21%
Other Respiratory Complications	39%
Renal Failure	20%
Other	20%

The adult respiratory distress syndrome without other complications was the cause of death of 21 percent of these patients. Of the 39 percent of patients who had other respiratory complications, death was attributable to some nonpulmonary complication, but respiratory failure was a terminal event. Thus, approximately 60 percent of deaths occurring in patients with pancreatitis are associated with pulmonary complications.

The multiple thoracic manifestations of pancreatitis are listed in Table 21.

TABLE 21

THORACIC MANIFESTATIONS OF PANCREATITIS

Pleural effusion
Pulmonary edema
Mediastinal pseudocyst
Bronchopleural fistula
Pancreatico-pleural fistula
Elevated and immobile diaphragm
Atelectasis
Hypoxemia
Pneumonia
Pulmonary emboli

Pleural effusion and pulmonary edema are the most important manifestations and will be reviewed. Mediastinal pseudocyst, broncho-pleural and pancreatico-pleural fistulas are rare but present important therapeutic considerations. Elevated and immobile diaphragms, atelectasis and resultant hypoxemia are extremely common but are non-specific manifestations of many acute abdominal processes. Pneumonia and pulmonary emboli occur frequently in association with pancreatitis and necessitate specific therapeutic intervention but are only indirectly attributable to pancreatitis.

B. Pleural Effusions

1. Incidence and characteristics

Pleural effusion in association with pancreatitis was initially described in 1901, and the significance of an elevated pleural fluid amylase was first appreciated in 1942. Since that time the clinical characteristics of typical pancreatic pleural effusions have been delineated, Table 22.

TABLE 22

CLINICAL CHARACTERISTICS OF PANCREATIC PLEURAL EFFUSIONS

Incidence	4 - 17%
Symptoms	Epigastric pain, nausea, vomiting, pleuritic pain (rare)
Radiographic	Usually small Left - 65% Bilateral - 20% Right - 15%

Pleural effusions have been reported in from 4-7 percent of patients with either acute or chronic pancreatic disease without other complications (75, 76). The symptoms are usually the epigastric pain, nausea and vomiting ascribed to the underlying pancreatic disease and only occasionally pleuritic pain. The effusion is commonly an incidental finding on routine chest X-ray. The effusions occur early in the disease and are usually small. They are left sided in 65 percent of cases, bilateral in 20 percent and right sided in 15 percent (75, 77, 78).

The characteristics of the pleural fluid are listed in Table 23.

TABLE 23

CHARACTERISTICS OF PANCREATIC PLEURAL EFFUSION FLUID

Protein	1.5 - 5.8 gms %
Specific Gravity	1.014 or greater
Appearance	Serosanguinous 65%
Amylase U/100 ml	
Serosanguinous	24,000
Serous	5,500

Protein concentrations range from 1.5 - 5.8 gms percent but the great majority of fluids have greater than 3.0 gms percent with a specific gravity of 1.014 or greater. Thus, the usual findings are

those of an exudate, and 65 percent are serosanguinous in appearance. Amylase concentrations, reported in Somogyi units/100 ml, are related to the character of the fluid. The mean amylase concentration in serosanguinous fluid is 24,000 with a range of 800 - 101,000 U/100 ml. Significantly lower concentrations are found in serous fluid. The mean amylase concentration in serous fluid is 5,500 with a range of 206 - 21,000 U/100 ml (79-81). Pleural fluid amylase is usually higher than serum amylase and pleural fluid amylase remains elevated after serum levels have returned to normal.

Pleural fluid amylase concentrations in effusions unrelated to pancreatic disease are consistently less than 200 U/100 ml and are always less than the serum amylase (77).

Pancreatic pseudocyst, pancreatic ascites, traumatic pancreatitis and pancreatico-pleural fistulas are associated with a much higher incidence of pleural effusions, Table 24 (82-87).

TABLE 24

INCIDENCE OF PLEURAL EFFUSIONS IN COMPLICATED PANCREATIC DISEASE

	Incidence	Reference
Pancreatic pseudocyst	21 - 50%	(82, 83)
Pancreatic ascites	20 - 27%	(84, 85)
Traumatic pancreatitis	50%	(86)
Pancreatico-pleural fistula	100%	(87)

Pleural effusions may occur in up to 50 percent of patients with pseudocyst or the more rarely encountered traumatic pancreatitis. Estimates in pancreatic ascites have varied between 20 to 30 percent, and fistulas invariably cause an effusion.

In contrast to the usual lack of symptoms with typical pancreatic pleural effusions, patients with more complicated disease frequently present with dramatic pulmonary symptomatology, Table 25.

TABLE 25

COMPLICATED PANCREATIC PLEURAL EFFUSIONS

Symptoms	Dyspnea, cough, severe chest pain, weight loss
Radiographic	Large, sometime massive effusions, left side not predominant, often bilateral

In contrast to patients with typical pancreatic pleural effusions, patients with a pseudocyst, pancreatic ascites, traumatic pancreatitis or a pancreatico-pleural fistula usually do not present with abdominal pain, nausea and vomiting (83, 84). Presentation of such patients with dyspnea, cough and occasionally severe pleuritic chest pain is common (86). Weight loss is a consistent finding (84). These effusions tend to be large to massive, recurrent and a left thorax location is not predominant. The fluid has several consistent findings, Table 26.

TABLE 26

CHARACTERISTICS OF COMPLICATED PANCREATIC PLEURAL EFFUSION FLUID

Appearance	Serosanguinous to bloody 80%
Protein	3.0 - 6.0 gm %
Amylase	24,000 - 108,000 U/100 ml

These fluids are almost always bloody and are frequently described as dark brown. The protein concentration is almost always greater than 3.0 gm percent, and amylase levels tend to be very high and seem to correlate with increased morbidity and perhaps mortality (88, 89).

Pancreatic abscesses with thoracic empyema or with chylous pleural effusions have also been reported but are distinctly uncommon. These fluids also have an elevation of the pleural amylase concentration (2, 90).

2. Differential diagnosis

Although an elevated pleural fluid amylase usually indicates pancreatic disease, other etiologies of a high pleural fluid amylase concentration must be considered, Table 27.

TABLE 27

POTENTIAL SOURCES OF PLEURAL FLUID AMYLASE

Direct
- Pancreatitis
- Pseudocyst

Neoplastic
- Bronchogenic carcinoma
- Pancreatic tumors
- Lymphoma/leukemia

Miscellaneous
- Empyema
- Esophageal rupture
- Idiopathic

Pancreatitis and pancreatic pseudocyst are the most common causes of elevated pleural fluid amylase concentrations. However, high levels have also been reported in bronchogenic carcinoma, pancreatic carcinoma and in lymphocytic leukemia and Hodgkins lymphoma. A study of 100 sequential pleural fluids found 13 with a high amylase concentration. Seven had lung cancer, three had cancer involving the pancreas and there were single cases of lymphocytic leukemia and Hodgkins disease (91). All cases of neoplastic disease had prominent lymphangitic spread of neoplasm in the lung, and it was postulated that the normal lymphatic flow of amylase was blocked leading to leakage into the pleural space. Among miscellaneous causes, one case of pneumococcal empyema was found to have a high amylase concentration in the above mentioned study. Additionally, elevated pleural fluid amylase occurs in esophageal rupture. Polyacrylamide gel electrophoresis has shown the amylase in this condition to be of salivary rather than pancreatic origin (92). Finally, a patient has been reported with a pleural fluid amylase of 53,000 U/100 ml, and a normal pancreas at laparatomy. No etiology was found, and the effusion eventually resolved (77). Thus, although pancreatogenic pleural effusion is the most common cause of a high pleural fluid amylase concentration, an elevated amylase is not pathognomonic of pancreatitis, and other diseases must be considered.

3. Theories of etiology

Three theories regarding the pathogenesis of pleural effusions have been presented, Table 28.

TABLE 28

THEORIES OF PATHOGENESIS OF PANCREATIC PLEURAL EFFION

Hematogenous enzyme transfer
Direct diaphragmatic enzyme transfer
Lymphatic enzyme transfer

The first theory is the hematogenous transfer of enzymes. It is postulated that pleural capillaries contiguous to an area of pancreatic inflammation become excessively permeable and that amylase rich pleural fluid is formed when serum with a high amylase concentration diffuses into the pleural space along a concentration gradient from pleural capillary blood to pleural space. The basis for the theory is the occurrence of fat necrosis secondary to pancreatic enzymes in sites distant from the pancreas in acute pancreatitis. Such fat necrosis has been noted in periesophageal, diaphragmatic, parietal pleura and subcutaneous fat. Further, pleural reactions have been produced by both intravenous and retroperitoneal injections of pancreatic enzymes. This theory fails to explain the higher concentration of amylase in pleural fluid than in blood.

A second theory postulates that enzyme rich fluid from the abdomen enters the chest via normal diaphragmatic communications around the esophagus, aorta, and vena cava. These channels communicate with the mediastinum, not with the pleural space. Thus, fluid must first collect in the mediastinum and subsequent pleural rupture must then occur to lead to an enzyme rich pleural effusion. Mediastinal collections of fluid have been observed with pseudocysts, but in most instances of usual pancreatitis mediastinal fluid is not found. Most authors believe this mechanism accounts for only a small percentage of pleural effusions seen in usual pancreatitis, but probably accounts for a majority of effusions seen with pseudocysts. Additionally, pseudocysts may cause direct diaphragmatic perforations with pancreatico-pleural fistulas.

The third theory postulates that pancreatitis leads to a collection of enzyme rich abdominal fluid which is transferred to the pleural space via lymphatics. The enzyme rich fluid diffuses through the peritoneal mesothelium into infradiaphragmatic peritoneal lymphatics. The fluid then traverses transdiaphragmatic lymphatics to the supradiaphragmatic parietal pleural lymphatics from which the fluid leaks into the pleural space because of increased lymphatic permeability. This theory is based on the well demonstrated existence of numerous lymphatic vessels which join the lymphatic network of the superior surface of the diaphragm with those of the inferior surface. The parietal pleura overlies the superior surface lymphatics and the peritoneal mesothelium overlies the inferior surface. The lymphatic transfer of substances from the abdomen to the thorax is well supported. Mixtures of graphite and pancreatin were injected intraperitoneally in rats and 18-48 hours later, areas of fat necrosis were found in areas corresponding to lymphatic channels as delineated by the graphite. Because lymphatics draining the left side of the abdomen traverse the left hemithorax, this theory explains the left sided predominance. Right sided or bilateral effusions could be accounted for by pancreatic tissue to the right of the midline. Most authors favor the lymphatic transfer theory as a mechanism for usual pleural effusions in pancreatitis (93).

4. Treatment

Pancreatic pleural effusion can best be approached by knowledge of the etiology of the pancreatic disease and the subsequent mechanism of formation of the fluid, Table 29.

TABLE 29

TREATMENT OF PANCREATIC
PLEURAL EFFUSION

1) None
2) Thoracentesis
3) Tube thoracostomy
4) Fistula ligation
5) Decortication

The usual small, asymptomatic, serosanguinous effusion of acute pancreatitis probably represents translymphatic enzyme transfer and resolves spontaneously without residua. Therefore it requires no treatment (75). When patients present with large symptomatic effusions direct diaphragmatic extension is likely. Evacuation of the pleural space should be attempted at the time of the initial thoracentesis (82). Because of the mechanism of initial formation, rapid reaccumulation is not unusual and requires tube thoracostomy. The enzyme rich highly exudative fluid may rapidly provoke a fibrinous pleuritis and necessitates drainage of the pleural space.

Pancreatic duct disruption or pseudocyst rupture may result in pancreatic-pleural fistulas. Pleural fluid drainage may exceed a liter per twenty-four hours. Even with fistula formation approximately fifty percent of patients demonstrate spontaneous closure with tube drainage alone. Surgical intervention is necessary in the remainder. Non-closure after two weeks of drainage is associated with an increase in mortality and is an indication for surgical fistula ligation (87).

In the occasional patient incomplete evacuation of pancreatic pleural effusion results in fibrous constricting pleuritis. In this situation decortication and pleuretomy are recommended to restore lung function (93).

In the rare case of pancreatic abscess the pleural fluid may be infected secondary to contamination with enteric organisms. Since these organisms include Bacteriodes as well as the coliforms pleural space drainage is best accomplished by rib resection (94).

C. Pancreatitis with ARDS

1. Incidence

Although pulmonary edema has been consistently described in approximately forty percent of patients dying with pancreatitis (2, 95) the realization that this entity is the adult respiratory distress syndrome has been only recently recognized (96, 97). An increasing awareness of the incidence and severity of hypoxemia has led to increased investigation in this field (98), Table 30.

TABLE 30

COMPARISON OF HYPOXEMIA IN PANCREATITIS TO OTHER ACUTE ABDOMINAL CONDITIONS

Lowest $Pa0_2$ (mm Hg)	Pancreatitis n = 84 (%)	Controls n = 68 (%)	Mortality of Pancreatitis (%)
70 or >	20	59	5.9
60 to 69	35	22	6.9
< 60	45	19	13.2

Imrie compared the degree of arterial hypoxemia in patients presenting with acute pancreatitis to a control group of pre-operative patients with a variety of acute abdominal emergencies. Over 80 percent of patients with pancreatitis had an arterial oxygen tension of less than 70 mm Hg while only 40 percent of those with acute abdomen presentations demonstrated that degree of hypoxemia. These data indicates that comparable degrees of abdominal pain causing chest splinting, diaphragmatic dysfunction and subsequent atelectasis could not explain the level of hypoxemia in patient with acute pancreatitis. Increasing severity of hypoxemia on presentation also correlated with increased mortality. When the arterial oxygen tension was less than 60 mm Hg the mortality was 13.2 percent and dropped to 5.9 percent with a tension of greater than 70 mm Hg (98). The recognition of the frequent finding of serious arterial hypoxemia in patients with pancreatitis lead to the description of the adult respiratory distress syndrome (99, 100), Table 31.

TABLE 31

ADULT RESPIRATORY DISTRESS SYNDROME
IN PANCREATITIS

Incidence	5 - 22%
Onset	2 - 7 days after onset of pancreatitis
Manifestations	Early-asymptomatic with mild to moderate hypoxemia Late-tachynea dyspnea anxiety worsening, hypoxemia bilateral alveolar infiltrates

This complication has been reported in from 5 to 22 percent of all patients with pancreatitis (96, 100, 101).

2. Clinical Syndrome

Diffuse pulmonary disease begins 2-7 days following onset of symptoms of pancreatitis and occurs more often in the severely ill patients with hypocalcemia and increased triglycerides (99, 100). Early in the course, the physical exam of the chest and chest X-ray are usually not helpful although blood gases will reveal hypoxemia. Nearly 100 percent of reported patients who developed respiratory distress are tachypneic with a P_aO_2 that ranges from 45-70 mm Hg. Hypoxemia and hyperventilation occur early in the course before infiltrates become manifest on chest X-ray. As the syndrome progresses, tachypnea, dyspnea, and anxiety increase and more profound hypoxemia develops. Chest X-ray reveals bilateral generalized alveolar infiltrates. Coincident with the onset of respiratory failure temperature and serum amylase often become elevated. The clinical and radiographic abnormalities may persist for 1-4 weeks (96, 97, 100). Mortality rate is similar to other patients with ARDS may be as high as 80 percent (101).

3. Physiologic Abnormalities

An increase in lung water has been demonstrated in patients who develop respiratory insufficiency and the physiologic hallmarks of pulmonary edema associated with pancreatitis have been delineated, Table 32.

TABLE 32

PHYSIOLOGIC HALLMARKS OF PULMONARY EDEMA IN PANCREATITIS

Decreased lung volumes
Decreased compliance
Increased dead space ventilation
Increased shunt
Normal PCWP, CVP, PVR
Increased cardiac index

Both lung volumes and compliance are decreased reflecting an increased stiffness of the lung. Dead space ventilation and shunt fraction are both increased. These abnormalities are due to an abnormal pattern of gas distribution in the lungs with closure of airways or alveoli or both, and an increase in pulmonary extravascular water (96, 102).

More recently patients studied with pulmonary edema have been shown to have a normal pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), and pulmonary vascular resistance (PVR). In a single patient the protein content of edema fluid was found to be 5.4 gms percent with serum protein of 5.8 gms percent. This finding suggests loss of integrity of capillary endothelium with exudation of plasma into the alveoli and interstitium as the cause of the increase lung water (100, 103).

4. Pathogenesis of Pulmonary Edema

The pulmonary edema has been attributed to a variety of events that occur in association with severe pancreatitis, Table 33.

TABLE 33

ETIOLOGIES OF PULMONARY EDEMA IN PANCREATITIS

Fluid overload with decreased oncotic pressure
Aspiration of gastric secretions
Hypotension
Disseminated intravascular coagulation
Direct products pancreatic inflammation

Patients with acute pancreatitis generally are alcohol abusers and tend to have a lower than normal serum albumin and thus a decreased plasma colloid oncotic pressure. As previously described this produces pulmonary edema at a lower pulmonary capillary wedge pressure. Fluid overload is present in some cases tending to increase pulmonary microvascular pressures potentiating pulmonary edema. However, the high protein content of the edema fluid suggests that this syndrome is a true ARDS due to increase pulmonary capillary permeability (100, 103).

Aspiration of low pH gastric secretions causes a clinical picture identical to the respiratory distress associated with pancreatitis. The frequent presence of vomiting, nasogastric intubation and obtundation in these patients suggest gastric aspiration as an etiologic event. However, the constant nasogastric drainage usually performed on these patients coupled with the delayed onset of the pulmonary edema makes this possibility unlikely but does not exclude a role for aspiration in the etiology.

A majority of cases of pulmonary edema due to pancreatitis have been in shock at sometime during their hospital course. However, most studies are unable to show that hypovolemic shock alone is sufficient to produce a syndrome of pulmonary edema.

Severe pancreatitis can be associated with disseminated intravascular coagulation (DIC) and DIC has been induced in animal models by the intravenous infusion of trypsin. Following infusion there is a decrease in platelets, fibrinogen, factor V and factor VIII associated with increased fibrinolytic activity of the plasma and increased prothrombin time (104, 105). Although frequently associated with pulmonary sequelae, DIC has never been consistently shown to occur in patients developing pancreatic associated pulmonary edema and its exact etiologic role is unclear.

While pulmonary edema may be related to these non-specific etiologies, there are also several products of pancreatic inflammation which may act directly on the lung, Table 34.

TABLE 34

PANCREATIC INFLAMMATORY PRODUCTS

Myocardial depressant factor
Fat embolus
Phospholipase A
Kallikrein
Trypsin

There is evidence that a myocardial depressant factor (MDF) is released during episodes of pancreatitis. Myocardial depressant factor has a negative inotropic effect on the left ventricle leading to elevated PCWP and pulmonary edema. Degenerative lesions of the myocardium have

been reported in patients with acute pancreatitis, and similar lesions can be induced in experimental animals (106). The MDF has been characterized as a polypeptide and both *in vitro* and *in vivo* myocardial depression has been shown. However, most clinical studies have found a normal PCWP and absence of signs and symptoms of heart failure. The entire concept of a myocardial depressant factor has recently been challenged and remains controversial (107).

Fat embolism is a well recognized cause of a pulmonary edema syndrome and fat emboli may be associated with pancreatitis. With pancreatitis, there is a peripheral digestion and stress mobilization of fat with increase in free fatty acids and triglycerides. The triglycerides may be further metabolized to free fatty acids. Experiments have demonstrated the local pulmonary toxicity of neutral fats and free fatty acids and it has been postulated that hydrolysis of fat emboli by lipase rich lung contributes to the pulmonary capillary damage (108). Although the relationship between hyperlipermia and pancreatitis is complex, serum levels of triglycerides have been elevated to the point of lactescence in the sera of patients with pancreatic associated pulmonary edema (100). This finding suggests that abnormal fat concentration may play a role in this disease.

Pharmacologic agents including Trypsin, Phospholipase A and Kallikrein are released in acute pancreatitis (109, 110). An attractive hypothesis for the genesis of pancreatic ARDS involves Phospholipase A which is a lecithinase, Figure 7.

FIGURE 7

PHOSPHOLIPASE A REACTION

$$\text{Surfactant} \xrightarrow[\text{A}]{\text{Phospholipase}} \text{Lysolecithin} + \text{Oleic Acid}$$

Lecithin is the principal component of surfactant and Phospholipase A splits one fatty acid off of lecithin to form lysolecithin and oleic acid. The concentration of this enzyme is increased 10-fold in pancreatitis and parallels elevation is serum amylase (111).

It has been postulated that Phospholipase A alters surfactant leading to unstable alveoli and eventually to alveolar and airway collapse (112, 113). Products of this enzymatic reaction are oleic acid and lysolecithin which have independent deleterious effects. Oleic acid is the prototype free fatty acid used to produce fat embolism. Lysolecithin disrupts the phospholipid layer of membranes and leads to altered membrane permeability and eventually to pulmonary edema (114). When administered intravenously, the enzyme localizes in the lungs and produced tachypnea, hypoxemia, and a decrease in pulmonary surfactant activity in dogs (112, 115).

Additionally both Trypsin and Kallikrein released from the pancreas activate Kallikreinogen resulting ultimately in kinin production (116), Figure 8.

FIGURE 8

KALLIKREINOGEN REACTION

$$\text{Kallikreinogen} \xrightarrow{\text{Trypsin}} \text{Kallikrein}$$

$$\text{Kinnogen} \xrightarrow[\text{Kallikrein}]{\text{Trypsin}} \text{Kinins}$$

A fall in precursor kinnogen levels has been demonstrated in the plasma of dogs with acute hemorrhagic pancreatitis (110). Kinin formation results in marked increased in vascular permeability which has obvious implications in formation of increased lung water.

5. Treatment

Treatment of pulmonary edema associated with pancreatitis is non-specific. The therapy is similar in all cases of non-cardiogenic pulmonary edema and frequently involves ventilatory support to provide adequate oxygenation and to decrease respiratory work. The association of DIC should be appreciated and bleeding complications treated appropriately. Nasogastric suction which decreases the stimulus for pancreatic enzyme production is most important in reversing the hypercoagulable state.

Trasylol, a kallikrein-trypsin inhibitor, has been evaluated in human subject as a treatment for acute pancreatitis. Evidence for a reduction in mortality is the most common parameter which has been monitored. Results have been conflicting but two controlled studies showed no difference in the treated versus control group (117, 118). There has been no evaluation of trasylol either prophylactically or therapeutically in patients with pancreatitis associated pulmonary edema.

I could find no controlled study evaluating the use of corticosteroids in the treatment of pancreatitis associated pulmonary edema. The role of steroids in the treatment of this syndrome remains controversial.

SUMMARY

Hepatic and pancreatic disease are frequently associated with pulmonary complications. These complications may be specific or non-specific. Prompt recognition of specific complications requires a knowledge of their pathogenesis. This review has attempted to present an approach to the etiology of the direct and indirect pulmonary complications of hepatic and pancreatic disease.

BIBLIOGRAPHY

1. Finley, J. W.: Respiratory complications of acute pancreatitis. *Am. Surg.* 35:591, 1969.

2. Gliedman, M. L., Bolooki, H., and Rosen, R. G.: Respiratory failure. *Curr. Probl. Surg.* 26:16, 1970.

3. Fluckiger, M.: Vorkommen von trommelschlagel-formigen Fingerendphalangen ohne chronische Veranderungen an der Lungen oder an Herzen. *Wien. Med. Wochenschr.* 34:1457, 1884.

4. Vanamee, P., Poppell, J. W., Glicksman, A. S., Randall, H. T., and Roberts, K. E.: Respiratory alkalosis in hepatic coma. *Arch. Intern. Med.* 97:762, 1956.

5. Snell, A. M.: The effects of chronic disease of the liver on the composition and physicochemical properties of blood: Changes in the serum proteins; reduction in the oxygen saturation of the arterial blood. *Ann. Intern. Med.* 9:690, 1935.

6. Rodman, T., Sobel, M., and Close, H. P.: Arterial oxygen unsaturation and the ventilation-perfusion defect of Laënnec's cirrhosis. *N. Engl. J. Med.* 263:73, 1960.

7. Tyor, M. P., and Sieker, H. O.: Biochemical, blood gas and peripheral circulatory alterations in hepatic coma. *Am. J. Med.* 27:50, 1959.

8. Calabresi, P., and Abelmann, W. H.: Porto-caval and porto-pulmonary anastomoses in Laënnec's cirrhosis and in heart failure. *J. Clin. Invest.* 36:1257, 1957.

9. Fritts, Jr., H. W., Hardewig, A., Rochester, D. F., Durand, J. and Cournand, A.: Estimation of pulmonary arteriovenous shunt-flow using intravenous injections of T-1824 dye and Kr^{85}. *J. Clin. Invest.* 39:1841, 1960.

10. Shaldon, S., Caesar, J., Chiandussi, L., Williams, H. S., Sheville, E., and Sherlock, S.: The demonstration of porta-pulmonary anastomoses in portal cirrhosis with the use of radioactive krypton (Kr^{85}). *N. Engl. J. Med.* 265:410, 1961.

11. Williams, Jr., J. H., and Abelmann, W. H.: Portopulmonary shunts in patients with portal hypertension. *J. Lab. Clin. Med.* 62:715, 1963.

12. Murray, J. F., Dawson, A. M., and Sherlock, S.: Circulatory changes in chronic liver disease. *Am. J. Med.* 24:358, 1958.

13. Rydell, R., and Hoffbauer, F. W.: Multiple pulmonary arteriovenous fistulas in juvenile cirrhosis. *Am. J. Med.* 21:450, 1956.

14. Sanders, J. S., and Martt, J. M.: Multiple small pulmonary arteriovenous fistulas. *Circulation* 25:383, 1962.

15. Berthelot, P., Walker, J. G., Sherlock, S., and Reid, L.: Arterial changes in the lungs in cirrhosis of the liver—lung spider nevi. *N. Engl. J. Med.* 274:291, 1966.

16. Ruff, F., Hughes, J. M. B., Stanley, N., McCarthy, D., Greene, R., Aronoff, A., Clayton, L., and Milic-Emili, J.: Regional lung function in patients with hepatic cirrhosis. *J. Clin. Invest.* 50:2403, 1971.

17. Silverstein, E.: Peripheral venous oxygen saturation in patients with and without liver disease. *J. Lab. Clin. Med.* 47:513, 1956.

18. Nakamura, T., Nakamura, S., Tazawa, T., Abe, S., Aikawa, T., and Tokita, K.: Measurement of blood flow through portopulmonary anastomosis in portal hypertension. *J. Lab. Clin. Med.* 65:114, 1965.

19. Gamal, M. E., Stoker, J. B., Spiers, E. M., and Whitaker, W.: Cyanosis complicating hepatic cirrhosis. Report of a case due to multiple pulmonary arteriovenous fistulas. *Am. J. Cardiol.* 25:490, 1970.

20. Hutchison, D. C. S., Sapru, R. P., Sumerling, M. D., Donaldson, G. W. K., and Richmond, J.: Cirrhosis, cyanosis and polycythaemia: Multiple pulmonary arteriovenous anastomoses. *Am. J. Med.* 45:139, 1968.

21. Moore, T. C., Normell, L., and Eiseman, B.: Histamine metabolism in isolated perfused canine liver. *Surg. Forum* 14:78, 1963.

22. Martini, G. A., Arndt, H., Baltzer, G., Buchta, I., Hardewig, A., Marsch, W., and Schmidt, H. A.: Pulmonary circulation in portal hypertension. *Ann. N. Y. Acad. Sci.* 170:280, 1970.

23. Said, S. I., and Mutt, V.: Polypeptide with broad biological activity: Isolation from small intestine. *Science* 169:1217, 1970.

24. Seymour, C. A.: Hepatogenous cyanosis and subarachnoid haemorrhage. *Proc. R. Soc. Med.* 69:59, 1976.

25. Robin, E. D., Laman, D., Horn, B. R., and Theodore, J.: Platypnea related to orthodeoxia caused by true vascular lung shunts. *N. Engl. J. Med.* 294:941, 1976.

26. Snell, R. E., and Luchsinger, P. C.: The relation of arterial hypoxemia to the hyperventilation of chronic liver disease. *Am. J. Med. Sci.* 245:289, 1963.

27. Heinemann, H. O., Emirgil, C., and Mijnssen, J. P.: Hyperventilation and arterial hypoxemia in cirrhosis of the liver. *Am. J. Med.* 28:239, 1960.

28. Karetzky, M. S., and Mithoeffer, J. C.: The cause of hyperventilation and arterial hypoxia in patients with cirrhosis of the liver. *Am. J. Med. Sci.* 254:797, 1967.

29. Schmidt, C. F., and Comroe, Jr., J. H.: Functions of the carotid and aortic bodies. *Physiol. Rev.* 20:115, 1940.

30. Tyler, J. M.: The effect of progesterone on the respiration of patients with emphysema and hypercapnia. *Clin. Res.* 5:229, 1957.

31. Tyler, J. M.: The effect of progesterone on the respiration of patients with emphysema and hypercapnia. *J. Clin. Invest.* 39:34, 1960.

32. Goodland, R. L., Reynolds, J. G., and Pommerenke, W. T.: Alveolar carbon dioxide tension levels during pregnancy and early puerperium. *J. Clin. Endocrinol.* 14:522, 1954.

33. Seeds, A. E., Battaglia, F., and Hellegers, A. E.: Effects of pregnancy on the pH, PCO_2, and bicarbonate concentrations of peripheral venous blood. *Am. J. Obstet. Gynecol.* 88:1086, 1964.

34. Whitmore, S., and Chiodi, H.: Progesterone, pulmonary hyperventilation and cirrhosis. *Ann. Intern. Med.* 77:326, 1972.

35. Casey, T. H., Summerskill, W. H. J., Bickford, R., and Rosevear, J. W.: Body and serum potassium in liver disease. II. Relationships to arterial ammonia, blood pH, and hepatic coma. *Gastroenterology* 48:208, 1965.

36. Schenker, S., McCandless, D. W., Brophy, E., and Lewis, M. S.: Studies on the intracerebral toxicity of ammonia. *J. Clin. Invest.* 46:838, 1967.

37. Hunt, S., Vaamondi, C. A., Rattazzi, T., Berian, M. G., Said, S. I., and Papper, S.: Circulating levels of VIP in liver disease. *Arch. Intern. Med.* In Press.

38. Vedel, S. N., and Puech, A.: Considerations surles entachements pleuraux au cours de la cirrhose de laennas. *Bull. Soc. Sci. Med. Biol. Montpellier* 8:120, 1927.

39. Morrow, C. S., Kantor, M., and Armen, R. N.: Hepatic hydrothorax. *Ann. Intern. Med.* 49:193, 1958.

40. Tumen, H. J.: Cirrhosis of the liver. In *Gastroenterology*, Volume 3, H. L. Bockus, ed., W. B. Saunders Co., Philadelphia, page 315, 1946.

41. Johnston, R. F., and Loo, R. V.: Hepatic hydrothorax. *Ann. Intern. Med.* 61:385, 1964.

42. Singer, J. A., Kaplan, M. M., and Katz, R. L.: Cirrhotic pleural effusion in the absence of ascites. *Gastroenterology* 73:575, 1977.

43. Falchuk, K. R., Jacoby, I., Colucci, W. S., and Rybak, M. E.: Tetracycline-induced pleural symphysis for recurrent hydrothorax complicating cirrhosis. *Gastroenterology* 72:319, 1977.

44. Rubinson, R. M., and Bolooki, H.: Intrapleural tetracycline for control of malignant pleural effusion: A preliminary report. *South. Med. J.* 65:847, 1972.

45. Yunis, E. J., and Moran, T. J.: Chylothorax and portal cirrhosis. *J. Am. Med. Assoc.* 192:150, 1965.

46. Cain, J. C., Grindlay, J. H., Bollman, J. L., Flock, E. V., and Mann, F. C.: Lymph from liver and thoracic duct. *Surg. Gynecol. Obstet.* 85:559, 1947.

47. Dumont, A. E., and Mulholland, J. H.: Alterations in thoracic duct lymph flow in hepatic cirrhosis: Significance in portal hypertension. *Ann. Surg.* 156:668, 1962.

48. Webster, B. H.: Pleuropulmonary amebiasis. *Am. Rev. Respir. Dis.* 81:683, 1960.

49. Sullivan, Jr., B. H., and Bailey, F. N.: Amebic lung abscess. *Dis. Chest* 20:84, 1951.

50. Ragheb, M. I., Ramadan, A. A., and Khalil, M. A. H.: Intrathoracic presentation of amebic liver abscess. *Ann. Thorac. Surg.* 22:483, 1976.

51. Ochsner, A., and DeBakey, M.: Pleuropulmonary complications of amebiasis. *J. Thorac. Surg.* 5:225, 1936.

52. Altemeier, W. A., Schowengerdt, C. G., and Whiteley, D. H.: Abscesses of the liver: Surgical considerations. *Arch. Surg.* 101:258, 1970.

53. Pitt, H. A., and Zuidema, G. D.: Factors influencing mortality in the treatment of pyogenic hepatic abscess. *Surg. Gynecol. Obstet.* 140:228, 1975.

54. Gross, P. A., and Gerding, D. N.: Pleural effusion associated with viral hepatitis. *Gastroenterology* 60:898, 1971.

55. Cocchi, P., and Silenzi, M.: Pleural effusion in HB_SAG-positive hepatitis. *J. Pediatr.* 89:329, 1976.

56. Tabor, E., Russell, R. P., Gerety, R. J., Barker, L. F., Hillis, W. D., and Jackson, D. R.: Hepatitis B surface antigen and e antigen in pleural effusion: A case report. *Gastroenterology* 73:1157, 1977.

57. Flaum, M. A.: Spontaneous bacterial empyema in cirrhosis. *Gastroenterology* 70:416, 1976.

58. Murray, H. W., and Marks, S. J.: Spontaneous bacterial empyema, pericarditis, and peritonitis in cirrhosis. *Gastroenterology* 72:772, 1977.

59. Trewby, P. N., Warren, R., Contini, S., Crosbie, W. A., Wilkinson, S. P., Laws, J. W., and Williams, R.: Incidence and pathophysiology of pulmonary edema in fulminant hepatic failure. *Gastroenterology* 74:859, 1978.

60. Sandweiss, D., and Thomson, B.: The adult respiratory distress syndrome: The predisposing role of liver disease. *Ariz. Med.* 30:264, 1973.

61. Gaar, Jr., K. A., Taylor, A. E., Owens, L. J., and Guyton, A. C.: Effect of capillary pressure and plasma protein on development of pulmonary edema. *Am. J. Physiol.* 213:79, 1967.

62. Rackow, E. C., Fein, I. A., and Leppo, J.: Colloid osmotic pressure as a prognostic indicator of pulmonary edema and mortality in the critically ill. *Chest* 72:709, 1977.

63. White, M. K., Shepro, D., and Hechtmann, H. B.: Pulmonary function and platelet-lung interaction. *J. Appl. Physiol.* 34:697, 1973.

64. Mummery, R. V., Bradley, J. M., and Jeffries, D. J.: Microbiological monitoring of patients in hepatic failure with particular reference to extracorporeal porcine liver perfusion. *Lancet* 2:60, 1971.

65. Finley, R. J., Holliday, R. L., Lefcoe, M., and Duff, J. H.: Pulmonary edema in patients with sepsis. *Surg. Gynecol. Obstet.* 140:851, 1975.

66. Blaisdell, F. W., Lim, Jr., R. C., and Stallone, R. J.: The mechanism of pulmonary damage following traumatic shock. *Surg. Gynecol. Obstet.* 130:15, 1970.

67. Ware, A. J., D'Agostino, A. N., and Combes, B.: Cerebral edema: A major complication of massive hepatic necrosis. *Gastroenterology* 61:877, 1971.

68. Scadding, J. G., Chronic diffuse interstitial fibrosis of the lungs. *Br. Med. J.* 1:443, 1960.

69. Turner-Warwick, M.: Fibrosing alveolitis and chronic liver disease. *Q. J. Med.* 37:133, 1968.

70. Doniach, D., Roitt, I. M., Walker, J. G., and Sherlock, S.: Tissue antibodies in primary biliary cirrhosis, active chronic (lupoid) hepatitis, cryptogenic cirrhosis and other liver diseases and their clinical implications. *Clin. Exp. Immunol.* 1:237, 1966.

71. Livingstone, J. L., Lewis, J. G., Reid, L., and Jefferson, K. E.: Diffuse interstitial pulmonary fibrosis. A clinical, radiological, and pathological study based on 45 patients. *Q. J. Med.* 33:71, 1964.

72. Lukash, W. M.: Complications of acute pancreatitis. Unusual sequelae in 100 cases. *Arch. Surg.* 94:848, 1967.

73. Foster, P. D., and Ziffren, S. E.: Severe acute pancreatitis. *Arch. Surg.* 85:252, 1962.

74. Gliedman, M. L., Bolooki, H., and Rosen, R. G.: Acute Pancreatitis. *Curr. Probl. Surg.* 26:3, 1970.

75. Kaye, M. D.: Pleuropulmonary complications of pancreatitis. *Thorax* 23:297, 1968.

76. Murphy, D., Duncan, J. G., and Imrie, C. W.: The "negative chest radiograph" in acute pancreatitis. *Br. J. Radiol.* 50:264, 1977.

77. Hammarsten, J. F., Honska, Jr., W. L., and Limes, B. J.: Pleural fluid amylase in pancreatitis and other diseases. *Am. Rev. Tuberc.* 79:606, 1959.

78. Fishbein, R., Murphy, G. P., and Wilder, R. J.: The pleuropulmonary manifestations of pancreatitis. *Dis. Chest.* 41:392, 1962.

79. Mitchell, C. E.: Relapsing pancreatitis with recurrent pericardial and pleural effusions. *Ann. Intern. Med.* 60:1047, 1964.

80. Bittar, E. E.: Amylase activity in hemothorax associated with pancreatitis. *Arch. Intern. Med.* 109:601, 1962.

81. Blumberg, L., and Stein, L.: Traumatic pancreatitis complicated by enzyme-containing pleural effusion. *S. Afr. Med. J.* 36:189, 1962.

82. Christensen, N. M., Demling, R., and Mathewson, Jr., C.: Unusual manifestations of pancreatic pseudocysts and their surgical management. *Am. J. Surg.* 130:199, 1975.

83. Rosenberg, I. K., Kahn, J. A., and Walt, A. J.: Surgical experience with pancreatic pseudocysts. *Am. J. Surg.* 117:11, 1969.

84. Hotz, J., Goebell, H., Herfarth, C., and Probst, M.: Massive pancreatic ascites without carcinoma. Report of three cases. *Digestion* 15:200, 1977.

85. Donowitz, M., Kerstein, M. D., and Spiro, H. M.: Pancreatic ascites. *Medicine* 53:183, 1974.

86. Roberts, J. C.: Traumatic pancreatitis and pleural effusion. *Aust. N. Z. J. Surg.* 45:90, 1975.

87. Cameron, J. L., Kieffer, R. S., Anderson, W. J., and Zuidema, G. D.: Internal pancreatic fistulas: Pancreatic ascites and pleural effusions. *Ann. Surg.* 184:587, 1976.

88. Miridjanian, A., Ambruoso, V. N., Derby, B. M., and Tice, D. A.: Massive bilateral hemorrhagic pleural effusions in chronic relapsing pancreatitis. *Arch. Surg.* 98:62, 1969.

89. Cochran, J. W., Pancreatic pseudocyst presenting as massive hemothorax. *Am. J. Gastroenterol.* 69:84, 1978.

90. Evans, H. W.: Painless chronic pancreatitis, chylo-ascites, and chylothorax. Report of a case. *Am. J. Med. Sci.* 240:494, 1960.

91. Ende, N.: Amylase activity in body fluids. *Cancer* 14:1109, 1961.

92. Sherr, H. P., Light, R. W., Merson, M. H., Wolf, R. O., Taylor, L. L., and Hendrix, T. R.: Origin of pleural fluid amylase in eosphageal rupture. *Ann. Intern. Med.* 76:985, 1972.

93. Shapiro, D. H., Anagnostopoulos, C. E., and Dineen, J. P.: Decortication and pleurectomy for the pleuropulmonary complications of pancreatitis. *Ann. Thorac. Surg.* 9:76, 1970.

94. Warshaw, A. L.: Pancreatic abscesses. *N. Engl. J. Med.* 287:1234, 1972.

95. Rovner, A. J., and Westcott, J. L.: Pulmonary edema and respiratory insufficiency in acute pancreatitis. *Radiology* 118:513, 1976.

96. Interiano, B., Stuard, I. D., Hyde, R. W.: Acute respiratory distress syndrome in pancreatitis. *Ann. Intern. Med.* 77:923, 1972.

97. Ranson, J. H. C., Roses, D. F., and Fink, S. D.: Early respiratory insufficiency in acute pancreatitis. *Ann. Surg.* 178:75, 1973.

98. Imrie, C. W., Ferguson, J. C., Murphy, D., and Blumgart, L. H.: Arterial hypoxia in acute pancreatitis. *Br. J. Surg.* 64:185, 1977.

99. McWilliams, H., and Gross, R.: Pancreatitis and the lungs. *Am. Surg.* 40:448, 1974.

100. Warshaw, A. L., Lesser, P. B., Rie, M., and Cullen, D. J.: The pathogenesis of pulmonary edema in acute pancreatitis. *Ann. Surg.* 182:505, 1975.

101. Palvik, R., Liigent, A., and Sissak, H. M.: Respiratory failure in acute pancreatitis. *Intensive Care Med.* 3:97, 1977.

102. DeTroyer, A., Naeije, R., Yernault, J. C., and Englert, M.: Impairment of pulmonary function in acute pancreatitis. *Chest* 73:360, 1978.

103. Hayes, Jr., M. F., Rosenbaum, R. W., Zibelman, M., and Matsumoto, T.: Adult respiratory distress syndrome in association with acute pancreatitis. Evaluation of positive end expiratory pressure ventilation and pharmacologic doses of steroids. *Am. J. Surg.* 127:314, 1974.

104. Robboy, S. J., Major, M. C., Colman, R. W., and Minna, J. D.: Pathology of disseminated intravascular coagulation (DIC). Analysis of 26 cases. *Hum. Pathol.* 3:327, 1972.

105. Kwaan, H. C., Anderson, M. C., and Gramatica, L.: A study of pancreatic enzymes as a factor in the pathogenesis of disseminated intravascular coagulation during acute pancreatitis. *Surgery* 69:663, 1971.

106. Vogel, F. S.: Cerebral demyelination and focal visceral lesions in a case of acute hemorrhagic pancreatitis with a consideration of the possible role of circulating enzymes in the causation of the lesions. *Arch. Pathol.* 52:355, 1951.

107. Wangensteen, S. L., Ramey, W. G., Ferguson, W. W., and Starling, J. R.: Plasma myocardial depressant activity (shock factor) identified as salt in the cat papillary muscle bioassay system. *J. Trauma* 13:181, 1973.

108. Peltier, L. F.: Fat embolism. III. The toxic properties of neutral fat and free fatty acids. *Surgery* 40:665, 1956.

109. Kellermeyer, R. W., and Graham, Jr., R. C.: Kinins - possible physiologic and pathologic roles in man. *N. Engl. J. Med.* 279:859, 1968.

110. Ofstad, E.: Kinins in acute hemorrhagic pancreatitis. *Scand. J. Gastrolenterol.* 5:9, 1970.

111. Editorial: Mechanism of pancreatic autodigestion. *N. Engl. J. Jed.* 283:487, 1970.

112. Morgan, A. P., Jenny, M. E., and Haessler, H.: Phospholipids, acute pancreatitis, and the lungs: Effect of lecithinase infusion on pulmonary surface activity in dogs. *Ann. Surg.* 167:329, 1968.

113. Zieve, L., and Vogel, W. C.: Measurement of lecithinase A in serum and other body fluids. *J. Lab. Clin. Med.* 57:586, 1961.

114. Reinitz, E. R., Motoyama, E., Smith, G. J. W., and Kerstein, M. D.: Pulmonary sequellae of experimental pancreatitis. *J. Surg. Res.* 22:566, 1977.

115. Kellum, Jr., J. M., DeMeester, T. R., Elkins, R. C., and Zuidema, G. D.: Respiratory insufficiency secondary to acute pancreatitis. *Ann. Surg.* 175:657, 1972.

116. Kellermeyer, R. W., and Graham, Jr., R. C.: Kinins - possible physiologic and pathologic roles in man. *N. Engl. J. Med.* 279:754, 1968.

117. Trapnell, J. E., Talbot, C. H., Chir, M., and Capper, W. M.: Trasylol in acute pancreatitis. *Am. J. Dig. Dis.* 12:409, 1967.

118. Dreiling, D. A., Leichtling, J. J., and Greenstein, A. J.: Trasylol revisited: The value of proteolytic inhibitors in the therapy of pancreastitis. *Mt. Sinai J. Med.* 43:409, 1976.