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Acute pancreatitis : a review of present day treatment with an analysis of the use of cortisone in therapy

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ACUTE PANCREATITIS
A REVIEW OF PRESENT DAY TREATMENT WITH AN ANALYSIS OF THE USE OF CORTISONE IN THERAPY.

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I. Introduction

Acute pancreatitis as an entity dates back to 1842 when an inflammation of the pancreas was described for the first time by Clausen. (58) Since that time a great amount of mystery has clouded the picture of acute pancreatitis. This uncertainty has not limited itself, but has extended into the fields of etiology, diagnosis and treatment. It will be the purpose of this paper to present a review of treatment used to date with an attempt to present a critical analysis of the newer use of the adrenal corticoids in the treatment of such. However, to present a more complete picture of this, a brief summary of proposed etiological theories and a note on clinical picture and diagnosis will be incorporated into this paper.

The first experimental pancreatitis was produced by Claude Bernard in 1856. (6) In this experiment, he injected a mixture of sweet oil and bile into the pancreatic duct of rats, causing them to die in about eighteen hours. Experiments similar to this were carried out by various men including Hlava (45) in 1890, Lancereaux (46) in 1899, and Polya (51) in 1906, in which the injecting agents were bile, gastric juice, intestinal juice, hydrochloric acid and calcium chloride. All of these agents resulted in the production of an acute hemorrhagic pancreatitis. Flexner (27) in 1900 reported the experimental production of pancreatitis by injecting acids, alkalies, bacteria and formalin.

Prior to that, Reginald Fitz (26 in 1889 wrote a paper that expresses the opinion of many authorities today. He stated that the inflammation probably originated by an extension of gastrointestinal inflammation along the pancreatic duct. He stated further that some cases may be induced by hemorrhage into the pancreas and that some may be traumatic in origin although it is usually of unknown origin. In 1901, Opie (49) presented what has since become the most popular of the many proposed theories. At an autopsy of a patient that had died following an acute abdominal crisis, a small gall stone was found snuggly filling the diverticulum of Vater. He proposed that this may occlude the common orifice of the bile duct and the duct of Wirsung and convert them into a continuous closed channel. The bile would then enter the pancreas by way of the pancreatic duct and the pancreas would become the seat of inflammatory change characterized by necrosis of parenchymatous cells, hemorrhage and accumulation of inflammatory products. He stated that anatomical pecularities of the diverticulum of Vater and the duct of Wirsung do not permit this sequence in all individuals who have gall stones. He proceeded to do experimental work and injected bile into the pancreatic duct of dogs, causing a necrotizing hemorrhagic inflammation of the pancreas resembling the lesion of human pancreatitis and like it accompanied by fat necrosis. He proposed that necrosis of the parenchymatous cells and hemorrhage represented the primary action

of the bile and the inflammatory reaction rapidly followed. Thus he arrived at the conclusion that the frequent association of cholelithiasis with hemorrhagic and gangrenous pancreatitis resulted in impaction of gall stones at the orifice of the diverticulum of Vater and penetration of bile into the pancreas.

Diagnosis of acute pancreatitis in its early days would have been far from easy. Fitz (26) stated that it was well characterized and was much more common than was generally thought. His diagnosis depended upon pain, tenderness and tympany in the region of the pancreas which was due to a localized peritonitis beginning in the epigastrium, one which occurred suddenly during ordinary health and without an obvious cause. This remained the basis of diagnosis until 1929 when Elman (24) presented his work on the value of blood amylase determinations in pancreatic disease. He suggested at that time that the determination would be of undoubted clinical value in excluding suspected disease and adding conclusive confirmatory evidence when the clinical picture is vague or indefinite. This has proven to be true and the serum amylase is the diagnostic factor in most cases of acute pancreatitis today. This test is quite specific, but may be elevated following the administration of morphine sulfate, with some renal insufficiencies, abdominal trauma or perforated viscus. (1) Symptoms that suggest the diagnosis include pain in any part of the abdomen present in 41% of the cases with extension through to the back present 30%

of the time, nausea and vomiting in 24% and jaundice in 19% of the cases in a series investigated by Heffernon and Cassiet.(32) Findings present on physical examination include abdominal tenderness, shock, rigidity that is often less marked than the catastrophic nature of the main would indicate, a mass in the region of the pancreas and distention. Radiographic findings of the abdomen may include localized areas of ileus as shown by the gas patterns, pancreatic calculi or gall stones. (32) In spite of this increased diagnostic acumen, the initial diagnosis is missed in 65% to 75% of the cases. (63)

Similar to etiology and diagnosis, the treatment of acute pancreatitis has had a slow progression over the years from its early beginnings to what it is now. However, there is still no widespread agreement regarding the treatment of choice. In 1889, Fitz (26) stated that pancreatitis was frequently confused with an acute obstruction, which he regarded as an indication for an early laparotomy. He stated that this was extremely hazardous in the early stages of an acute pancreatitis and that treatment should be nothing but paliative. He suggested that the possibility of the successful removal of the gangrenous pancreas was to be considered due to the healthy condition of a patient seventeen years after he had discharged this organ from his bowels. This early advocation of conservative therapy in the acute phase had also been presented by Korte in his paper in 1894, but in 1910 was obliged to reverse his decision and advocated early

operation. (66) By 1920 the accepted treatment of choice was surgical and the various procedures that were being done were cholecystectomy, cholecystostomy, choledochostomy, drainage of the pancreas and lesser omentum and sphincterotomy.(38,43,66) These procedures were recommended as soon as the shock was relieved. By 1940, there was again a wide difference of opinion, with the majority feeling that an acute abscess resulting from pancreatitis should be drained but that an acute hemorrhagic pancreatitis should be operated upon only if the diagnosis were in doubt. (47) Drainage of the gall bladder apparently was indicated if the patient were jaundiced. Treatment of shock and fluid balance was being recognized as very important and it was recommended to disturb the pancreas as little as possible as, due to its anatomical structure, it could not be drained adequately by merely splitting the capsule.

Indications for surgical treatment is not well agreed upon at the present time. Godfrey (28) states that a cholecystostomy in the acute stage is useless unless a stone can be removed from the common duct. Some of the indications for surgical intervention are absence of a diagnosis in an acute abdomen, an obstruction resulting in jaundice, ruptured gall bladder or persistent spreading peritonitis. (15,29,42,58)

The medical management of this problem will be discussed at greater lengths later in this paper.

II. A Review of Present Theories of Etiology

The volume of literature written on the etiological agents of acute pancreatitis is massive. This would tend to indicate that no one factor can be singled out as a primary cause, but it also indicates that there is apparently quite a bit that is not known or is only vaguely known. This review will not thoroughly discuss all theories that have been presented to this time, but to give an over-all picture of the current trend in thinking.

Opie's (49) theory of an obstruction resulting in a common channel is probably the most widely accepted theory. Causes of this obstruction may be gall bladder disease, sphincter spasm, edema, epithelial plaques, ascaris, tumors or pancreatic calculi. (9) Statistics showing the relationship of pancreatitis and gall bladder disease would seem to confirm this thought. Ivy and Gibbs (35) found that there was cholelithiasis in 55% of 667 patients, acute cholecystitis in 18% of 238 and a normal gall bladder in 30% of 125. They also reported there being acute pancreatitis present in 18% of the cases of acute cholecystitis. Other workers (8,32) have stated that pancreatitis is associated with gall bladder disease from 30 to 46% of the time. However, as it is pointed out by Bristow, (9) the incidence of acute pancreatitis is greater in males than in females while the opposite is true of cholecystitis. The importance of this is not commented on but may be due to other factors to be presented.

Raising some doubt as to the finality of the common channel theory is the fact that of 2,004 cases, only 5% were found to have a stone obstructing the ampulla of Vater. (56) Mann and Giordano (45) found the pancreatic duct and common bile ducts entering the duodenum by a common opening in 20% of 200 routine autopsies and add that in only 3.5% would a common channel be a reasonable possibility.

Doubilet (18,20) states that spasm is the key to the etiology of inflammatory disease of the biliary and pancreatic duct systems, but that its true incidence cannot be known. He says that this increase in its tonus (or spasm) is produced primarily by frustrating emotional disturbances, exhaustion, pain in other parts of the body, painful distention of the common bile duct, hydrochloric acid or alcohol in the duodenum, parasympathomimetic drugs, opiates or irritation of the colon.

Doubilet,(18) Ivy and Gibbs, (35) Powers (54) and Stein (68) all state that bile present in the pancreatic ducts will not produce a pancreatitis unless there is also a rupture of the ducts or a temporary obstruction to the outflow of pancreatic secretions. Powers (54) produced a pancreatitis by an intravenous injection of trypsin but it is only when both factors, i.e. obstruction and trypsin, that pancreatitis will regularly develop. He further states that obstruction leads to high levels of interstitial trypsinogen which may be converted to an active enzyme within the

pancreas resulting in a pancreatitis. Stein (68) also considers the possibility of trypsinogen activation but also states that the level of an antitrypsin factor may play an important part.

So then a review of the probable sequence of events in an obstruction is that the trypsin is activated by some activator or possibly by rupture of small ductules due to the increased pressure. This allows pancreatic juice to come into direct contact with blood vessels and pancreatic tissue. This results in edema, vascular necrosis or fat necrosis with the characteristic inflammatory changes following.

Other factors which are postulated as being relatively uncommon causes by Richman (58) include hyperlipemia, diabetic acidosis, malnutrition, pregnancy, hemochromatosis, trauma which may be either accidental, surgical or electrical, vascular which may be either arterial or venous occlusion and allergic. Wapshaw (72) considers the possibility of a neurogenic basis, Rich and Duff (57) present the possibility of ductal epithelial metaplasia causing an obstruction while Johnson (36) and Nemir (48) state that a toxic substance may be formed from a reaction between ischemic blood and pancreatic juice.

The possibility of pancreatitis being a disease of adaptation was presented by Selye (61) in 1950. He subjected animals to various types of stressful situations and produced experimental lesions similar to those of acute pancreatitis in man. On the

basis of the frequent and pronounced involvement of the pancreas both during acute and chronic exposure to stress, he proposed that comparable pancreatic lesions in man may find their explanation in derailments of the adaptive mechanisms.

Kaplan (40) is also a proponent for the acceptance of pancreatitis being a disease of adaptation. He presents an analogy of a Cushing's ulcer being caused by an ischemic necrosis of the wall of the stomach following emotional trauma and so proposes that the same thing could occur in the pancreas, as the two organs are similar in embryology, nerve and blood supply. He states that the body reacts to systemic damage (shock) with a systemic defense mechanism (counter shock). The resistance put forth depends on nervous, humoral influences, degree of shock, previous exposure and previous adaptation. The adrenals react by increasing their production of mineralocorticoids, regardless of the stress. The proposed change in vascular network of the pancreas is based on the experimental change following DOCA and desoxycortisone administration. This change consisted of edema, necrosis and inflammation followed by secondary scarring and fibrosis.

Kaplan (40) tends to discount the association of gall bladder disease, in that it is more common in females while pancreatitis is from three to six times more common in males. He attributes the association to a colic stress in addition to the physical factor resulting in the common channel. He also implicates

physical trauma, infections, overindulgence and toxic agents as stress and states that alcoholism is associated with emotional distress. He cites pancreatitis following transurethral prostatic resections and mastoidectomies as probably being due to a systemic stress. His theory may then be summarized as stress leading to arteriolar spasm of the target organ which causes the tissue ischemia with pathological changes that vary from the edema to necrosis and gangrene that is present in acute pancreatitis.

Starr (67) presents a somewhat different view point. He suggests that the thyroid adrenal axis may be of importance in the pathogenesis of certain abdominal conditions of unknow etiology including pancreatitis. The development of pancreatic obstruction presents many of the features of a metabolic disorder allied to the collagen diseases. The slow progress with crises, the indeterminate histology ranging from edema to fibroblastic infiltration and fibrosis and the associated involvement of other structures resemble the picture of this group of disorders. The involvement may be diffuse or localized and may be invoked by dietary excess, stress, infective or psychological and hormonal (menstrual) disturbances.

A number of articles have been written recently that would indicate that cortisone therapy may be a cause of acute pancreatitis. Bencosme (3), Lazarus and Bencosme (44), Stumpf (70) and Volk and Lazarus (71) all conducted similar experiments in which hyperplasia

and hypertrophy of the pancreatic ductular system and hyperplastic and dilated ducts were frequently found following adrenal corticoid administration. Focal areas of pancreatic necrosis, peripancreatic necrosis and granulomatous inflammation were also seen. The similarity to the pathology seen in ductal ligation suggests an obstructive nature and Bencosme (3) suggests that changes in viscosity may be of importance but states also that it is possible that high levels of steroids exert a direct stimulation to the ductal epithelium similar to other steroids action of tissues such as breast or prostate. Cattell and Warren (12) present experimental evidence that cortisone can cause a temporary decrease in the volume output of the pancreas, but do not speculate on this being a possible cause of pancreatitis.

Pancreatitis has also been reported in humans who have been treated with cortisone. Baar and Wolff (2) reported two cases of pancreatic necrosis in children associated with corticoid therapy, one of which was being treated for asthma and the other for dermatomyositis. Hypersensitivity, mechanical obstruction, epithelial metaplasia, dietary imbalance and infection were not thought to play any part in either of these cases but rather a peculiar constitutional disposition whose nature is obscure. The theory was proposed that cortisone has an effect on pancreatic secretion and that in the presence of the previously mentioned

unknown constitutional disposition this causes a stagnation of secretions and pancreatic necrosis by reflux mechanism.

Carone and Liebow (11) report casual observations of autopsy material suggests increased frequency of necrosis and other lesions of the pancreas and adjacent tissue in patients receiving certain steroids or ACTH. ACTH, cortisone, hydrocortisone, prednisone and prednisolone alone or in combinations were associated with the pancreatic lesions. These lesions consisted of acute pancreatitis or peri-pancreatic fat necrosis or both. These were reported as usually focal and mild. Diffuse or hemorrhagic pancreatitis was not seen and no definite symptoms or signs of pancreatitis were recorded clinically. Selye (62) agrees that pancreatitis with liponecrosis may occur in patients treated with large doses of cortisone or its derivatives.

III. A Review of Present Day Treatment

Haubrich (30) says that the correct management of a suspected case of pancreatitis begins with the drawing blood for an amylase determination. In making this diagnosis and instituting the medical management that it implies, it is very important to be accurate as most acute abdomens fall in the realm of surgical management. (1)

Although dissenting opinions continue to be expressed, the prevailing one is one of conservatism. (4) Even though a distinction was made in 1933 by Elman (23) between the then well known acute hemorrhagic pancreatitis and a less fulminant acute edematous pancreatitis, this distinction is not important concerning the treatment and many times is impossible to make. (4) Once the diagnosis is made, the treatment must be energetic even though it is to be conservative. However, Comfort (15) states that in milder attacks, presumably those due largely to edema, the need for control of pain often is the major and sometimes the sole indication for treatment.

The consensus of nearly all writers is that medical management is the treatment of choice in acute pancreatitis. As stated previously, surgery is limited to those cases in which there is no diagnosis in an acute abdomen or in an obstruction with jaundice. (37) Bockus (8) states that surgery is completely contraindicated if an acute pancreatitis is suspected. On the other

hand, Jones (37) says that surgery is relatively harmless providing the manipulation of the pancreas is held to a minimum.

Jones (37) divides the medical management into the following categories, which will be the outline used in this review: 1) control of pain, 2) management of shock, fluids and electrolyte imbalances, 3) decreasing pancreatic secretions, 4) gastrointestinal tract distention, 5) suppurative complications, 6) carbohydrate metabolism disturbances, 7) surgical complications, and 8) recurrences.

(a) Control of Pain

The pain of acute pancreatitis may be very agonizing and unrelenting and its relief can be very important. This pain, if unrelieved, can cause a reflex vasoconstriction with the resultant pancreatic ischemia, thus setting up a sequence of events resulting in a continuous cycle. (37) The opiates of which morphine sulfate, dihydromorphine hydrochloride (Dilaudid) and meperidine hydrochloride (Demerol) may be mentioned are theoretically contraindicated in that they tend to induce duodenal and ductal spasm. (4) As Demerol is the least spasmogenic of these, it is probably the choice of these three agents. (30) A dosage of 100 to 150 mg every three to four hours is usually necessary to be effective in the relief of the pain. (37) If morphine is to be used, its dose is usually 10 to 15 mg every three to four hours and the dosage of Dilaudid would be two to four mg every

three or four hours if it is to be used. (37) Nitrites may be useful and probably diminish pain directly by relaxing smooth muscle reducing duodenal and ductal spasm and may also tend to overcome vasoconstriction. (4) The action of these would be very short in duration but may be given as inhalations of a pearl of amyl nitrite or tablets of glyceryl trinitrate sublingually. (4) Other antispasmodics that have occasionally been used include aminophylline, papaverine and calcium gluconate. (37) The other less potent centrally acting analgesics as codeine, ASA or other newly developed ones are useful when the pain is of a nature that may be controlled by these agents. (17) Barbiturates given as phenobarbital may also be useful in controlling the pain. (42) Tetraethylammonium chloride may be effective in some cases where narcotics are not. (4) This agent blocks the sympathetic and parasympathetic impulses at the ganglionic synapse but does not block the painful afferent stimule from the gastrointestional tract. Its action is prbably due to reduced secretory activity both directly and due to decreased acid secreted by the stomach resulting in a lessened secretion of secretin in the duodenum and thus a lessened stimulation of the pancreas. Its action may also reduce the tone of the sphincter as a result of a vagal block. Hypotension and other distressing side reactions detract from its usefulness. (4)

Procaine hydrochloride has been used in several ways for the relief of pain. Paravertebral blocks are used extending from a level of the tenth thoracic vertebrae up to the fourth. (17) A block of the splanchnic ganglia may also be used. (4) This may tend to diminish vasoconstriction in the gland, but there may also be a further drop in blood pressure in an already shocky patient. This may also have a direct effect in decreasing pancreatic secretions. (4) This is administered initially on the side where the pain is the most severe, but one must frequently block both sides due to the pattern of enervation of the pancreas. One may get somatic nerve fibers also in the block, so an occasional peripheral parasthesia is to be expected. (4) Continuous epidural procaine has also been used. (1) Intravenous procaine has also been used, but is probably dangerous and not reliable.(37) The dosage has been recommended at four mg/kg in a 0.1% solution. Its duration is variable, but it may last for hours. It is proposed (4) that it possesses local anesthetic, analgesic and antihistaminic actions in addition to having vasodilatation and spasmolytic actions. However, when given intravenously, it is rapidly hydrolyzed indicating that possibly a degradant, dimethylaminoethanol may be responsible for the action. If this is to be used, great caution must be exercised. Toxic symptoms such as excitment, restlessness, dizziness, irritability, numbness, muscular twitching, skin reaction or dyspnea must be watched for.

A barbiturate should be on hand for instant intravenous administration as an antidote if toxicity develops. (4)

(b) Management of Shock, Fluids and Electrolyte Imbalances

Treatment here consists of the intravenous administration of whole blood, plasma, albumen, plasma expanders, normal saline or 5% glucose in distilled water or normal saline. Probably most important of these is the administration of whole blood. The purpose of this treatment is to restore blood volume, maintain blood pressure and to insure adequate urinary output. (4, 17, 58) Indiscriminate administration of glucose should be avoided because of impared carbohydrate metabolism. Fluid volumes should total between 2,000 and 3,000 cc per day unless there is an anuria and then volumes should be limited to about 1,000 cc per day in the form of 10% glucose water. (42) Norepinephrine may be given in amounts of 4 mg per 1,000 cc of 5% glucose water but the vasoconstriction that is produced may not be desirable. (30) It is in this field of the treatment of shock that some workers feel the use of adrenal corticoids has its basis.(1,15,37,58) However, this will be discussed at a later point.

Sodium and potassium are the two electrolytes that one is to be primarily concerned with. Surprisingly, large amounts of calcium may be transferred from the serum to areas of fat necrosis so that soaps are formed from the hydrolyzed fats, which in addition to other mechanisms such as excretion of calcium into

the bowel may contribute to the production of a hypocalcemia. (4) This may produce neuromuscular alterations and even cause myocardial abnormalities. The degree of hypocalcemia bears a close relationship to the severity of the disease and is of definite prognostic import. (4) Kelley (42) states that the hypocalcemia should be corrected if the serum level falls below 7 to 8 mg%. This should be corrected by the administration of 10 to 20 cc of 10% calcium gluconate intravenously each day until a normal level is reached. Dolan (17) says that any deficiency should be corrected by giving 150 mg of calcium per milligram drop in the serum level of calcium. The potassium level is also to be watched closely, especially when losses are likely to be considerable as when nasogastric suction is being used. (4) Here too there may be neuromuscular or myocardial manifestations in addition to the possibility of a hypokalemic alkalosis. (42) The indication for replacement here is a serum level of below 3 mEq/L which is to be attempted with caution if there is any indication of renal failure. (42)

(c) Decreasing Pancreatic Secretions

Attempts to attain this goal are directed primarily into three methods. These are: 1) nothing by mouth, 2) nasogastric suction, and 3) depression of nervous influences capable of stimulation of either the stomach or pancreas. The first two of these can usually be carried out without too much

difficulty. Their mechanism of action lies in the fact that the hormonal stimulus of the pancreas, secretin, is elaborated within the duodenal mucosa. This is in response to the stimulus of acid (optimum pH 4) which is provided by the contents of the stomach passing into the duodenum. (30) An antacid used intermittently with suction may have some value in decreasing this acid stimulus. A mechanical stimulus in the lumen of the duodenum probably contributes to the activation of secretin which is another reason for giving nothing by mouth. The depression of the nervous stimulus to the stomach or pancreas is attempted primarily through cholinergic blocking agents. (17) Methantheline bromide in doses of 50 to 100 mg every four to six hours in a continuous intravenous drip may be used. (42) This may also have an analgesic action due to overcoming spasm and reducing hypertonicity of the sphincter. (4) Another action that may help provide analgesia is the blocking of the pain from sympathetic afferent fibers. (42) Atropine is also used in doses of 0.6 mg every four to six hours. The action of this drug is probably due to producing a decreased secretion of secretin rather than a direct action of the pancreas itself. Side effects may include dryness of the mouth, thirst and possible bradycardia. (4) Phenobarbital may be used as a mild general sedation which will reduce nervous excitation and also depress pancreatic secretion. (4,37) Sympathomimetic drugs inhibit secretion, perhaps by decreasing the blood flow through the gland. That

effect and the vasoconstriction probably responsible for it are definite deterrents to the use of these drugs. (4) Ephedrine sulfate is the one used most often. Its dosage is from 25 to 50 mg every four to six hours.

Attempts have also been made along other lines of approach to diminish pancreatic secretions. In 1952 Rauch and Stenstrom (55) reported on experimental work in which pancreatic secretions were diminished following irradiation of the pancreatic area. In 1954 Heacock and Cara (31) reported on the clinical use of x-ray and advocated that it be used in conjunction with supportive measures for all cases of pancreatitis. The possibility of the use of a carbonic anhydrase inhibitor, Diamox, was studied by Dreiling. (21) He observed that adequate inhibition can not only block response to secretin but also suppress the basal output of the pancreas without effecting the secretion of the enzymes. He speculated that this might have theraputic implications if a control of volume at a cellular level were desired. Apparently this work has never been followed up or expanded. Pfeffer (50) reported that ACTH or hydrocortisone had no effect on lowering the volume of pancreatic secretions, so its use in treatment, which will be discussed later does not have this function as its basis.

(d) Gastrointestinal Tract Distention

Although this is believed by some men to constitute a specific area of treatment (1,4), its management is automatically

incorporated in that treatment designed to diminish the hydrochloric acid stimulation of secretin in the duodenum. This treatment referred to is the intermittent or continuous nasogastric suction previously referred to. The indication for treatment of this type is suggested by the fact that localized areas of ileus as indicated by the gas patterns of the small bowel is used as a diagnostic criterion by some men. (32,8)

(e) Suppurative Complications

This type of treatment is directed primarily toward secondary infections of peritonitis, (4) but is of primary importance if one suspects the etiology to be that of a bacterial infection. (16) The usual method of providing the prophylactic coverage that is desired is by using a combination of penicillin and streptomycin, (8,17,37) however, Berk (4) states that aureomycin and oxytetracycline appear to be the antibiotics of choice for this use. Although not definitely in the role of a suppurative complication, the attempts for control of fat necrosis will be briefly discussed here. The use of a crystalline soybean trypsin inhibitor was reported in several experimental studies in 1952 and 1953. (33,60) These investigators were not favorably impressed with the results of their experiments. Hoffman (33) reported a 50% mortality in his series of control dogs and a mortality of 50.8% in those treated with the trypsin inhibitor. Popper and Necheles (52) reported in 1953 that the intraperitoneal administration of sodium

formaldehyde sufoxylate lowered the occurrence of experimental fat necrosis from 85 to 38% and concluded that the result was possibly due to inhibition of tryposin or of lipase or of both. Later in 1953 Popper and Necheles (53) conducted another experiment on the use of quinine sulfate in preventing pancreatic fat necrosis in a series of 13 dogs. They reported a marked effect and stated that this was probably due to inhibition of pancreatic lipase. In 1955 Wapshaw (72) referred to this type of treatment by stating that theoretically a substance which is capable of arresting the activity of trypsin either in the gland or blood stream is likely to be beneficial but reminds one of the difficulty of arriving at a diagnosis early enough to institute treatment that would be successful.

(f) Carbohydrate Metabolism Disturbances

This was also previously referred to in the recommendation to avoid indiscriminate administration of glucose because of impared carbohydrate metabolism. (4) Shallenberger (63) reported that 20% of a series of 45 survivors of acute pancreatitis subsequently developed a permanent diabetes mellitus and that he believes that insulin should be given to control the hyperglycemia, when it is present. He felt that this exerted a protective effect and seemed to lessen the severity of the subsequent diabetes. Dolan (17) states that when insulin is used to control the hyperglycemia it must be followed by intermittent fasting blood glucose

determinations. Berk (4) sets the dosage of insulin at 5 to 10 units of regular insulin per 50 gm glucose, administered simultaneously with the glucose water preparation. He also adds that a hypoglycemia is to be avoided in that it is a potent vagal stimulus. Associated with this might be the maintainence of nutrition with protein hydrolysates when oral intake is prohibited over a prolonged period. (42)

(g) Surgical Complications

Quoted indications for surgical treatment are quite variable. That of the acute phase has been previously covered. Complications such as cysts, abscesses and hematomas may be operated on but it is much better if it can be done after the acute phase is over. (1,42) After recovery from the acute episode, a study of the biliary tract for associated disease should be carried out and a cholecystectomy or other indicated surgery may be done at this time. (5) Elective surgery is not indicated unless gall bladder pathology is revealed. (1)

(h) Recurrences

Ivy and Gibbs (35) found that 61% of their cases have a history of previous attacks, so the importance of preventing recurrences is readily pointed out. In presenting a figure as high as that, it would appear that there is no satisfactory way of preventing recurrences or else that a few people tend to have the attacks repeatedly. The usual routine is one of gradual

withdrawal of treatment as indicated by the clinical signs, i.e. pain, temperature, pulse and abdominal distention. (37) The resumption of oral intake begins with water, broth, milk and soups (37,42) and progresses to a frequent feeding, low fat, high protein, high carbohydrate and low residue diet. (42,58) Of considerable importance in the prevention of recurrences is avoiding over eating, obesity and alcohol. (58) Antacids, mild sedation may also be continued for an indefinite length of time. (37)

IV. A Review of the Use of Cortisone

As previously presented, Selye (61) was the first to suggest that cortisone might be effective in the treatment of acute pancreatitis. In his experimental work, he found that chronic treatment of rats with toxic doses of desoxycorticosterone acetate could cause especially pronounced vascular changes in the pancreas, which in the acute stage tended to produce edema, pancreatic necrosis and inflammatory changes while later phases resulted in scar formation with fibrosis. He also found that these changes could be prevented with cortisone.

The rationale of the use of cortisone has never been definitely established. It is referred to by some men only as an adjuvant in the course of the shock therapy that they are carrying out. (17,37,58) Elman (22) states that the only physiologic justification for the use of cortisone is the idea that cortisone is an "anti-inflammatory steroid" and that perhaps in an acute pancreatitis the inflammatory reaction is too great for the body to cope with. Kelly (42 has a similar attitude but suggests that there is a theoretical disadvantage in that evidence exists that the administration of cortisone can be harmful in the presence of a bacterial infection as is suspected in such as tuberculosis. Kaplan (41) proposes that the rationale have its basis in the pituitary stimulation of the adrenal cortex production of three types of steroid hormones, mineralocorticoids (aldosterone), glucocorticoids

(hydrocortisone, cortisone and cortiosterone) and sex hormones. He then refers to Selye's (61) statement that mineralocorticoids and glucocorticoids are antagonists and are normally in balance but that there is a disproportion in this relationship in all diseases. This is a response to a nonspecific stressor that may be mechanical, thermal, chemical, infectious or emotional and whose principal pathways are through the hypothalamic, pituitary, adrenal axis. Kaplan (41) feels that these nonspecific stressor agents initiate a vascular response that results in constriction, ischemia, thrombosis and tissue necrosis but that this chain of events can be interrupted by the use of cortisone which then allows the normal body defense mechanisms to take over.

The number of cases of acute pancreatitis that have been reported when treated with adrenal corticoids has been relatively few. Stephenson (69) reported the first case in 1952. His patient was a 25 year old white female that had had recurrent right upper quadrant pain of three years duration. She had had nausea, vomiting and pain radiating through to the back for five days prior to admission. On admission she appeared acutely ill, had a temperature of 103,8°F., a blood pressure of 120/70, was perspiring freely and appeared near shock. Findings included a tender and rigid right upper quadrant of the abdomen, a white count of 18,200, hemoglobin of 70% and a hematocrit of 35%. The diagnosis of acute cholecystitis was made and therapy was instituted consisting of

passing a Levin tube with Wangansteen suction and antibiotics consisting of 400,000 units of penicillin intramuscularly two times a day, 0.5 gm dihydrostreptomycin intramuscularly two times a day and 500 mg aureomycin intravenously daily. The temperature continued to increase, reaching 106°F., the respirations became rapid and the pulse weak. The patient was placed in Trendelenburg position and transfusions were started. Phenylephrine hydrochloride 0.1%, 3000 cc 5% glucose water and 1000 cc blood were given. The systolic blood pressure was between 50 and 60 and later was not obtainable as was neither the pulse. At this time 100 mg cortisone was given intramuscularly and was repeated six hours later. The pulse then returned and the blood pressure was 94/84. Twelve hours later an additional 100 mg cortisone was given. The patient then appeared more alert, but had evidence of a peritonitis. A laparotomy was done and bloody fluid was found in the abdominal cavity with areas of fat necrosis in the omentum which were biopsied. The patient continued to progress through a relatively uneventful post-operative course and was dismissed in good condition.

Other cases that have been reported have a similar story. The next man to report a case treated with cortisone was Hoste (34) who reported in 1953 a case of a fulminating pancreatitis in a 45 year old man that was associated with a hepatitis. The patient was comatose before treatment and then had a remarkable and rapid improvement. In 1955 Eskwith (25) made a comprehensive report of a 40 year old male who was diagnosed as having acute pancreatitis

on the basis of a serum amylase of 390 units but did not respond to medical treatment over a three-day period but was then started on 300 mg cortisone per day on the rationale that it might decrease the edema, exudate or inflammation that might be present. He reported that the pain had diminished in 24 hours and the temperature was normal in 48 hours. The patient was maintained on cortisone for 17 days, receiving a total of 3700 mg. Post morbid studies in this patient revealed a normal gall bladder. Eskwith pointed out that the response of the patient to the cortisone in the dramatic change in personality, relief of pain and return on appetitie could not be adequately described on paper. Solem (64) reported a case in 1955 in which the patient was treated with ACTH and responded very well but had a mild recurrence when the ACTH was withdrawn on the third day of its usage. It was then reinstituted and gradually withdrawn at a latter day with no recurrence reported. He stated that it was apparently anti-inflammatory on the basis of suppressing a progressive cellular damage and thereby the chain reaction which follows an inflammatory stimulus. He felt that the successful use of cortisone in thyroiditis, (13) orchitis (65) and hepatitis (14) might lead one to suspect that it might be useful in the treatment of pancreatitis.

Bloodworth and Cohen (7) also report one case that failed to respond to the usual form of medical but had a "dramatic improvement" following the initial use of 100 mg cortisone followed by

50 mg every six hours for a period of three days. Brockis and Jones (10) report the use of two cases which they stated were severely ill, apparently dying of vascular collapse that had been refractory to plasma and saline. They too experienced a relapse with withdrawal and respond to return to treatment with cortisone. Rogers (59) was prompted to use cortisone by the occurrance of four successive deaths due to acute hemorrhagic pancreatitis. He reported the use of cortisone in six patients of which he stated that there were two dramatic recoveries with the other four making satisfactory recoveries. The total dosages of prednisone varied from 275 to 500 mg. Kaplan (39) reports the use in nine patients of which he had 100% recovery. It is of interest to note that no fatalities were recorded in any of these reported cases; however, Kaplan (39) stated that three fatalities had been brought to his attention in patients that had been treated with cortisone.

Kaplan (41) states that there is no way of estimating the proper dose of cortisone or its equivalent of a similar substance. He starts his patients on 300 mg prednisone every 24 hours and adjusts the dosage as indicated. Dolan (17) uses 300 to 400 mg cortisone daily with a gradual decrease until there is a complete withdrawal at six days. He and Aaron (1) state that the dosage can be followed by doing eosinophile counts in that a failure to decrease the total number indicates that the dosage is inadequate.

The study of the use of cortisone in pancreatitis is far from being over and its true usefulness is not yet definitely established. This is exemplified by some additional work of Selye (62) who in 1958 stated that cortisone failed to prevent an experimental purulent pancreatitis that had been caused by subcutaneous injections of stylomycin aminonucleoside. He stated that the cortisone probably actually aggravated the pancreatitis because of the enhancement of pancreatic fat necrosis by aiding the spread of pathogenic organisms or by increasing the spread of pancreatic juices.

The present status of the use of cortisone in the treatment of pancreatitis is summed up in an editorial in the British Medical Journal (73) in which it recognizes that the beneficial clinical effects that have been reported contradict laboratory evidence. It is possible that steroids produce an intermittent obstruction due to a viscosity change, but that an acute hemorrhagic pancreatitis is a very rare complication of cortisone therapy in man and there is no reason for withholding it when the seriousness of the situation leads one to believe that it is indicated.

V. Summary

Following a brief introduction to and history of acute pancreatitis, a review of the present theories of the etiology of this disease was presented. The common channel theory of Opie was presented as the most widely accepted theory and some statistics were quoted that would both tend to uphold and to disprove this mechanism as being the primary cause. Various modifications and expansions of this theory were also brought out. Other possible etiological agents that were mentioned include infection, alcohol ingestion, hyperlipemia, diabetic acidosis, malnutrition, pregnancy, hemochromatosis, trauma, vascular, allergic, neurogenic and a ductal epithelial metaplasia causing obstruction.

Selye's work on the possibility of pancreatitis being a disease of adaptation was also reviewed. He found that alarming stimuli could cause focal necrosis of the pancreas in experimental and proposed that the extraordinarily frequent and pronounced involvement of the pancreas both during acute and chronic exposure to stress suggest that comparable pancreatic lesions in man may find their explanation in derailments of the adaptation mechanism. He found also that treatment of rats with DOCA could cause pronounced vascular changes in the pancreas which resulted in edema, pancreatic necrosis, inflammatory changes and scar formation. Kaplan proposed an analogy of a Cushings ulcer of the stomach being caused by an ischemic necrosis and thinks that the same thing could

occur in the pancreas as the two organs are similar in embryology, nerve and blood supply. He feels that the adrenals react to stress by increasing their production of mineralocorticoids which results in a change in the vascular network of the pancreas which causes the pancreatitis. However, several articles were reviewed in which experimental was thought to be caused by the administration of adrenal corticoids. Articles were also reviewed in which it was felt that pancreatitis in humans had been caused by the use of cortisone.

The discussion of the medical treatment is divided into the following categories: 1) control of pain, 2) management of shock, fluids and electrolyte imbalances, 3) decreasing pancreatic secretions, 4) gastrointestional tract distention, 5) suppurative complications, 6) carbohydrate metabolism disturbances, 7) surgical complications, and 8) recurrences. The methods used in each of these categories is discussed in the content of the paper. The recent use of cortisone is also discussed. It is pointed out that some men use it as an adjuvant in the treatment of shock but that others feel that it has a more physiological indication. Its effect as an anti-inflammatory agent is pointed out and Selye's and Kaplan's theory of increased mineralocorticoid production being antagonized by the administration of cortisone is also discussed. Reports of 22 cases of acute pancreatitis that had been treated with cortisone were reviewed and the usual

pattern seemed to be that of an acute, fulminant illness in which the patient was nearly moribund when the use of cortisone was instituted. Responses to this treatment were reported as miraculous, dramatic and other glowing adjectives. The contradiction between clinical and laboratory evidence is pointed out, but that in view of the clinical responses recorded, there is no reason for withholding cortisone at this time.

VI. Conclusion

In reviewing a series of articles on acute pancreatitis, one conclusion that may be fairly well established is that nothing real definite has ever been established along the lines of etiology or treatment. Of the many theories of etiology that have been advanced, the oldest and still the most widely accepted is the common channel as proposed by Opie in 1901, although many possible causes of the common channel are now recognized. This, although probably the most plausible theory certainly cannot be accepted as the cause in all cases. Evidence of this is the number of theories that have been proposed, each probably being the cause in an undeterminable number of cases. Similar to etiology, a definite pattern of treatment has never been established. The accepted methods of treatment today covering the eight points previously covered certainly cannot be considered as the optimum treatment when one looks at statistics concerning mortality and recurrence. The use of cortisone in treatment has been extremely favorable in the cases thus reported; however, the evidence of experimental and human pancreatitis being caused by cortisone administration certainly cannot be overlooked. I feel that the present status should be not that of routine administration in every case of pancreatitis, but that the patient should be treated in the what is now considered routine manner with the use of cortisone being reserved for those that do not respond to this type of treatment. I feel

that there is definitely no contraindication to its use when the pancreatitis is progressing and not responding to the above described medical management.

BIBLIOGRAPHY

1. Aaron, A. H. and Milch, Elmer, Acute Pancreatitis, Med. Clin. of North America, 40:451 (March) 1956.

2. Baar, H. S. and Wolff, O. H., Pancreatic Necrosis in Cortisone Treated Children, Lancet. 1:812 (April) 1957.

3. Bencosme, Sergio and Lazarus, Sidney, The Pancreas of Cortisone Treated Rabbits, Arch. Path. 62:363 (May) 1956.

4. Berk, J. Edward, Management of Acute Pancreatitis, J.A.M.A. 152:1 (May) 1953.

5. _____, Acute Pancreatitis, J. Mich. St. Med. Soc. 56:489 (April) 1957.

6. Bernard, Claude, Lecons de Physiologie Expermentale, Paris, 2:278, 1856.

7. Bloodworth, Augustus F. and Cohen, Stanley L., Cortisone in Treatment of Acute Pancreatitis Associated with Mumps Epidemic Parotitis, U. S. Armed Forces M. J. 7:285 (Feb.) 1956.

8. Bockus, H. L., Acute Inflammation of the Pancreas, Gastroenterology, 34:3 (March) 1958.

9. Bristow, William H., Acute Pancreatitis, Med. Times, 83:1248 (Dec.) 1955.

10. Brockis, J. G. and Jones, E. T., Treatment of Acute Hemorrhagic Pancreatitis with Cortisone, Brit. M. J. 2:1524, 1956.

11. Carone, Frank A. and Liebow, Averill A., Acute Pancreatic Lesions in Patients Treated with ACTH and Adrenal Corticoids, New Eng. M. J. 257:690 (Oct.) 1957.

12. Cattell, Richard B. and Warren, Kenneth W., Surgery of the Pancreas, Philadelphia, W. Saunders Company, pp 20, 1953.

13. Clark, D. E. and others, Subacute Nonsuppurative Thyroiditis Treated with Cortisone, J.A.M.A. 151:551, 1953.

14. Colbert, J. W. and others, The Use of ACTH in Viral Hepatitis, New England J. M. 245:172, 1951.

15. Comfort, Mandred W., Treatment of Pancreatitis, Arch. of Int. Med. 95:735 (May) 1955.

16. Delphia, Robert E., Acute Pancreatitis, J. Kan. Med. Soc. 58:396 (June) 1957.

17. Dolan, H. S. and Hopkirk, J. F., Acute Pancreatitis, Can. M. J. 69:495, 1953.

18. Doubilet, Henry J., Discussion of Chronic Relapsing Pancreatitis, Proc. of the Royal Soc. of Med. 50:629 (Sept.) 1957.

19. _____, Symptomatology and Treatment of Pancreatitis, Maryland M. J. 7:7 (Jan.) 1958.

20. _____, Recurrent Acute Pancreatitis, Ovservations on Etiology and Surgical Treatment, Ann. Surg. 128:609 (Oct) 1948.

21. Dreiling, David A., The Effect of a Carbonic Anhydrase Inhibitor Diamox on Human Pancreatic Secretion, Gastroent. 29:262 (Aug.) 1955.

22. Elman, Robert, Discussion of Symposium on Pancreas by Drs. Baker and Boles, Sullivan, Healy and Knight and Elliot, Zollinger, Moore and Ellison, Gastroent. 28:588, 1955.

23. _____, Acute Interstitial Pancreatitis, Surg. Gynec. and Obst. 57:291, 1933.

24. _____, et al, Value of Blood Amylase Estimation in Diagnosis of Pancreatic Disease, Arch. Surg. 19:943 (Dec.) 1929.

25. Eskwith, Irwin S. and others, Acute Hemorrhagic Pancreatitis Treatment with Cortisone, New. Eng. M. J. 252:494 (March) 1955.

26. Fitz, Reginald, Acute Pancreatitis, Bost. M. and S. J. 120:229 (March) 1889.

27. Flexner, Simon, Experimental Pancreatitis, Johns Hopkins Hospital Report, 9:743, 1900.

28. Godfrey, Norman, Acute Pancreatitis, Brit. M. J. 1:203 (Feb.) 1946.

29. Guzzo, Carl P., Acute Pancreatitis, J. of Med. Soc. of N. J. 54:108 (March) 1957.

30. Haubrich, William S., The Rational Management of Acute Pancreatitis, Ohio St. M. J. 51:1085, (Nov.) 1955.

31. Heacock, C. H. and Cara, D. J., Radiation Therapy of Pancreatitis, Radiology, 62:654 (May) 1954.

32. Heffernon, Elmer W. and Cassiet, Alfredoc, A Survey of Acute Hemorrhagic Pancreatitis, Gastroent. 35:3 (Sept.) 1958.

33. Hoffman, H. L. and others, Use of crystalling Soybean Trypsin Inhibitors in Acute Hemorrhagic Pancreatitis in Dogs, Arch. Surg. 66:617 (May) 1953.

34. Hoste, O., Pancreatitis bij Infectieuse Hepatitis, Behandeling met Cortisone, Belg. Tijdschr geneesk 9:492 (Dec.) 1957. Cited by: Kaplan, Murrel, Am. J. of Dig. Dis. 2:696 (Dec.) 1957.

35. Ivy, A. C. and Gibbs, G. E., Pancreatitis - A Review, Surg. 31:614 (April) 1952.

36. Johnson,Thomas A. and Kaiser, Martin H., The Pancreas: Contributions of Clinical Interest in 1956, Gastroent. 34:543 (April) 1958.

37. Jones, Charles A., Medical Management of Pancreatitis, Arch. Int. Med. 96:332, 1955.

38. Jones, Daniel Fiske, Acute Pancreatitis, Bost. M. and S. J. 186:337 (March) 1922.

39. Kaplan, Murrel H., ACTH and Cortisone in Gastroenterology, Am. J. of Gastroent. 27:162, 1957.

40. _____, Acute and Chronic Relapsing Pancceatitis - Clinical Implications of Their Acceptance as Diseases of Adaptation, Am. J. of Gastroent. 25:234 (March) 1956.

41. _____, Steroid Therapy in Acute Pancreatitis, Am. J. of Dig. Dis. 2:696 (Dec.) 1957.

42. Kelley, Maurice, Jr., Treatment of Acute and Chronic Pancreatitis, G.P. 12:105 (Nov.) 1955.

43. Kemp, Robert C., Diseases of the Stomach, Intestines and Pancreas, Philadelphia, W. B. Saunders, pp 1015, 1917.

44. Lazarus, Sydney and Bencosme, Sergio, Development and Regression of Cortisone Induced Lesions in Rabbit Pancreas, Am. J. Path. 26:1146 (Oct.) 1956.

45. Mann, A. C. and Giordano, H. S., The Bile Factor in Pancreatitis, Arch Surg. 6:1, 1923.

46. Lancereaux, E., Traite des Maladies du foie et du Pancreas, Paris, 1899. Cited by Mann

47. Morton, John J. and Widger, Stanley, The Diagnosis and Treatment of Acute Pancreatitis, Ann. Surg. 111:851 (May) 1940.

48. Nemir, Paul, Jr. and Drabkin, David L., The Pathogenesis of Acute Necrotizing Hemorrhagic Pancreatitis - An Experimental Study, Sur. 40:171 (July) 1956.

49. Opie, Eugene, The Etiology of Acute Hemorrhagic Pancreatitis, Johns Hopkins Hospital Bull. 12:182 (June) 1901.

50. Pfeffer, Robert B. and Hinton, J. William, Some Relationships Between Adrenal Medullary and Cortical Substances and Exocrine Functions of the Pancreas in Man, Gastroent. 31:746 (Dec.) 1956.

51. Polya, E. A., Zur Pathogenesis der Acuten Pankreasblutung und Pankreasnekrose, Berl. klen Wehnschr 93:1562, 1906.

52. Popper, H. L. and Necheles, H., Prevention of Pancreatic Fat Necrosis, Surg. Gyn. and Obst. 96:299 (March) 1953.

53. _____, Prevention of Pancreatic Fat Necrosis by Enzyme Inhibitors, Surg. 33:896 (June) 1953.

54. Powers, Samuel R. and others, The Pathogenesis of Acute and Chronic Pancreatitis, Ann. Surg. 142:690 (Oct.) 1955.

55. Rauch, Robert F. and Stenstrom, K. Wilhelm, Effects of X-ray Radiation on Pancreatic Function in Dogs, Gastroent. 20:595 (April) 1952.

56. Raudin, I. S. and Johnson, C. G., The Etiology and Pathogenesis of Acute Hemorrhagic Pancreatitis, Am. J. Med. Sci. 205:277 (March) 1943.

57. Rich, A. R. and Duff, G. L., Experimental and Pathological Studies on Pathogenesis of Acute Hemorrhagic Pancreatitis, Johns Hopkins Hospital Bull. 58:212, 1936.

58. Richman, Alexander, Acute Pancreatitis, Am. J. of M. 21:246.

59. Rogers, N. C. and others, Treatment of Acute Pancreatitis with Cortisone, Lancet. 2:651, 1956.

60. Rush, Benjamin and Cliffton, Eugene E., The Role of Trypsin in the Pathogenesis of Acute Hemorrhagic Pancreatitis and the Effect of an Antitryptic Agent in Treatment, Surg. 31:349 (March) 1952.

61. Selye, Hans, The Physiology and Pathology of Exposure to Stress, Montreal, ACTA, Inc., 1950.

62. _____, Effect of Anti-Inflammatory Hormones upon the Pancreatitis Produced by Stylomycin Aminonucleoside, Am. J. of Gastroent. 29:87 (Jan.) 1958.

63. Shallenberger, Paul L. and Kapp, David F., Acute Pancreatitis - A Clinical Review of 72 Attacks Occurring in 54 Patients, Ann. Int. Med. 48:1185 (June) 1958.

64. Solem, Jan H. and others, Treatment of Acute Pancreatitis with Cortico-Depot, ACTA Chirurgica Scancinavica 109:415 (Oct.) 1955.

65. Solem, J. H., The Effect of Corticotropin in Orchitis of Mumps, ACTA Med. Scandinava, 149:341, 1954.

66. Starr, F.N.G. and others, Report of 2 Cases of Acute Pancreatitis, Can. M.A.J. 11:182 (March) 1921.

67. Starr, Kenneth W., The Modern Approach to Pancreatitis, West. J. of Surg., Obst. and Gyn. 63:501 (Aug.) 1955.

68. Stein, Arthur and others, Experimental Hemorrhagic Pancreatitis - New Concepts of Pathogenesis, Ann. Surg. 143:508 (April) 1956.

69. Stephenson, Hugh E., Acute Hemorrhagic Pancreatitis, Arch. Surg. 65:307 (Aug.) 1952.

70. Stumpf, Harry H. and Wilens, Sigmund L., Pancreatic Lesions and Peripancreatic Fat Necrosis in Cortisone Treated Rabbits, Am. J. Path. 31:563 (May) 1955.

71. Volk, Bruno W. and Lazarus, Sydney S., The Effect of Various Diabetogenic Hormones on the Structure of the Rabbit Pancreas, Am. J. Path. 34:121 (Jan.) 1958.

72. Wapshaw, Henry, The Pathogenesis of Acute Pancreatitis, Glasgow Med. J. 36:76 (March) 1955.

73. Editorial, British M. J., 5066:333 (Feb.) 1958.