1963

Role of steroids in acute pancreatitis

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THE ROLE OF STEROIDS IN ACUTE PANCREATITIS

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Submitted in Partial Fulfillment for the Degree of
Doctor of Medicine

College of Medicine, University of Nebraska

April 1, 1963

Omaha, Nebraska

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I. Introduction

The most common disorder affecting the exocrine portion of the pancreas is inflammation of the pancreas, pancreatitis. There are generally three recognizable types. The initial inflammation is acute pancreatitis. Repeated transitory inflammation of the pancreas is recurrent acute pancreatitis. The previous two forms of disease lead to chronic pancreatitis.

The episodes of acute pancreatitis, either recurrent or initial, also vary in their severity. The edematous type is the mildest and, next in severity is the hemorrhagic type and finally one may also see the necrotic type. In any attack of acute pancreatitis one usually sees a combination of all three degrees of severity with one type usually being dominant. The inflammatory process may proceed to destroy most of the gland, or become arrested at any stage of destruction. (1) (14)

Acute pancreatitis is one of the few abdominal catastrophes in which conservative medical management is more effective than surgical intervention. This disease has heretofore often been refractory to any type of therapy. Patients with this disease before 1946 died early in the disease process from circulatory collapse, while in those treated after 1946 survival was longer and death resulted most frequently from secondary hemorrhage and sepsis. This was due to the rapid advances made in using intravenous fluids for circulatory collapse during World War II.

There still remains an apparently irreducible mortality, in the severe forms of this disease, which is in the neighborhood of 10 per cent. It is because of the previously stated reasons that great responsibility for the correct diagnosis of this disease rests with the physician. Even after the diagnosis there is still no definite form of therapy that will in most cases produce remission in the disease. In the last decade the use of glucocorticoids in the acute stages of this disease has been advocated by some because of the good therapeutic results obtained. However, there are also some who have evidence that steroids, mineralcorticoids and glucocorticoids, as well as ACTH may cause pancreatitis. (20) (26) (28)

II. Pathogenesis

Since the original description by Opie in 1901 on the etiology of acute pancreatitis, when he described a case of acute hemorrhagic pancreatitis due to a stone impacted at the ampulla of Vater, great effort has been made by pancreatic physiologists to construct a unified concept of the pathogenesis of inflammation within the pancreas. As of yet there has been no universally satisfactory explanation for the pathogenesis of acute pancreatitis. (14)

Obstruction to the outflow of pancreatic juice was thought to be the main cause of pancreatitis throughout the years in the eyes of most physiologists. However, obstructive causes other than gallstones have been considered. Edema and spasm of the

pancreatic duct, the duodenum and sphincter of Oddi are now considered to account for the majority of cases in which obstruction is a factor. Such things as alcohol, methanol poisoning, mumps, descending infections of biliary tract, extension of inflammation from a duodenal ulcer or diverticulum, stimulation of parasympathetics, and allergies have been claimed to have caused obstruction. Metaplasia of the pancreatic ductal epithelium has caused obstruction in some cases. Hyperlipemia and hyperparathyroidism are two situations which have also been associated with acute pancreatitis. Ivy and Gibbs [28] in their study of 2004 cases from literature found that stones were present at the papilla of Vater in only 5 per cent of cases. Other investigators have come up with similar figures although the number of cases reviewed have not been nearly as many as those of Ivy and Gibbs.

Nabatoff has advanced the theory that if obstruction is the cause then the pancreatic duct should be found dilated at autopsy. His own investigations did not reveal such correlation. Carone later showed some changes suggesting dilated ductules in autopsies of patients who had been on steroids. [10]

McCutcheon [34] gives the following experiments as evidence against his theory:

1. "Experiments designed to produce maximum secratory activity in the presence of complete duct obstruction have uniformly failed to produce pancreatic necrosis." (Thal 1957)

2. "Obstruction of the major pancreatic duct in cats, dogs, and rabbits causes atrophy of acini with preservation of the islets of Langerhans, not pancreatitis." (Wang 1958, Becker and Shaefer 1957).

3. "A marked raise in serum amylase level does not necessarily mean pancreatitis, and may be produced by drugs causing spasm of the sphincter of Oddi, without pancreatitis." (Gross 1951, Pfeffer 1953).

4. "The major pancreatic duct was ligated deliberately in 17 patients with chronic relapsing pancreatitis, and in none of these did severe pancreatitis develop during the immediate postoperative period." (Howard and Jordan 1960).

The other popular concept has been the vascular theory. Adequate blood flow is the most important factor in prevention of auto-digestion characteristic of acute pancreatitis. Therefore vascular spasm with resulting ischemia to the pancreas would produce the very circumstances most favorable for autolysis of the pancreatic tissue. The description of stress as a factor in causing acute pancreatitis has gained some acceptance over the last decade.

Since ischemic necrosis with hemorrhage can occur in the stomach after a stressful situation, there does not seem to be any reason why similar lesions could not occur in the pancreas because embriologically it is an anlage of the upper gut and it derives its nerve and blood supply from the same sources as does the stomach and duodenum. Impairment of the vascular supply seems just as reasonable an explanation of edema, hemorrhage and tissue necrosis in the pancreas as in the stomach.(28)

Viewing acute pancreatitis as a disease of adaptation to a

stress situation may clarify what happens in this disease. Stress produces a systemic reaction. This reaction is mediated by humoral and/or nervous factors. It results in systemic damage and calls forth a systemic defense reaction. The resistance produced by the body against this stress depends, in turn, upon a number of factors. Nervous and humoral influences, the degree of shock produced by the stress, previous exposure to the same stress and previous adaptation to it play a part in this particular situation of stress. No matter what form the stress may take, and no matter what the degree of response to it may be, the adrenal glands react by an increased production of mineralcorticoids. (28) (43)

Specifically in acute pancreatitis, Selye has shown that chronic treatment of rats with toxic doses of these hormones (desoxycorticosterone acetate and desoxocortisone) cause pronounced vascular changes in the pancreas. The edema, inflammatory changes and necrosis of the acute stage are succeeded later by scar formation and fibrosis. Stimulation of the cervical and thoracic nerve chains and some drugs act as stress agents and produce the same changes. No matter what agents or forces produce these changes, they can be prevented by the experimental administration of the glucocorticoid (cortisone). (28) (43)

If pancreatitis is regarded as a disease of adaptation a great deal that has been confusing about its etiology ceases to be obscure. Gallbladder disease fits logically into the picture.

It is much more common in females, but pancreatitis is 3 to 6 times more frequent in males. If gallstone collic is viewed as a stress factor as well as a physical factor in the production of this disease then the total exposure to stress situations and not sex, becomes the important factor. Similarly physical trauma, infection, over indulgence in food and the ingestion of other toxic agents may all be regarded as alarm stimuli. The combination of any of these agents with tension and nutritional deficiencies would provide a perfect setting for the genesis of acute pancreatitis. Alcoholism, which is often a partner to emotional distress is frequently implicated as a cause of acute pancreatitis. Thus alcohol sought at a time when the patient faces a conflict would only add to the stress through the irritation of the mucosa of the gastrointestinal tract. Savage has also shown that inflammatory disease of the pancreas can be associated with emotional disturbances. Also the increasing incidence of pancreatitis as a postoperative complication fits into this theory of adaptation because acute pancreatitis has occured after transurethral resection of the prostate and after mastoidectomies as well as operations in the region of the pancreas involving some direct trauma to the pancreas. Thus stress seems to take part in the production pancreatitis although such factors as obstruction at the ampulla of Vater may initiate the collic causing the stress response. (28)

There are also some other possible causes of acute pancreatitis

based on the vascular theory. The pancreatitis could be caused by venous thrombosis producing wet gangrene, rupture of an arteriosclerotic artery with pancreatic apoplexy could be a cause, as could delayed coagulation of blood or a vasomotor dyscrasia. Also experiments on dogs have shown that acute interstitial hemorrhagic and necrotic lesions occur in the portions of the gland in which the blood supply was altered by injection of metallic mercury into one of the pancreatic arteries. This type of necrosis which results from vascular damage is a specific autodigestion characteristic of acute pancreatitis.

III. Pathophysiology

The pancreas is considered to have greater activity per gram of tissue than any other abdominal organ. Normally the pancreas secretes between 800 to 1000 cc's per twenty-four hours, but under stimulation this may go up to 500 cc's per a two-hour period. This secretion is made up mostly of water (98%) and the rest are enzymes and bicarbonate.(31)

Pancreatic secretions are regulated by hormones formed by the mucosa of the upper portions of the small intestine. These secretions are produced by food products and irritants entering the small intestine. Secretin is released in response to acid, amino acids and digestion products of fat. Secretin affects only the secretion of bicarbonate and water, leaving the rate of secretion of enzymes unaltered. Amino acids, soap and acid cause the release of pancreozymin which in turn stimulates the

production of the pancreatic enzymes. Trypsin and chymotrypsin are secreted as inactive precursors, trypsinogen and chymotrypsinogen. Trypsinogen is activated by enterokinase, a product of the glands of the small intestine, or trypsin while chymotripsinogen is activated by trypsin. This activation for the most part takes place in the small intestine. A small portion of the protease pancreatic juice is at times present in the active form in the pancreatic ducts, and the amount of this activated form is increased when the juice has a high enzyme concentration. Both the pancreatic gland and pancreatic juice contain a low-molecular-weight protein which is a specific inhibitor of trypsin and which is inactivated in the intestinal lumen possibly by enterokinase. At the present time very little is known about elastase or collagenase, which have only been recently described. The digestive enzymes are secreted by the acinar cells while the water and bicarbonate are secreted by the interlobular ducts. (16) (23)

Cholinergic impulses from the vagus nerves stimulate mainly enzyme secretions-decreased volume with increased enzyme concentration, as well as causing contraction of the smooth muscle of the ducts. Stimulation of the sympathetics results in constriction of small blood vessels in the pancreas. (23)

The mode of entry of pancreatic enzymes into the tissue spaces of the pancreas is not completely understood. Even in the normal intact pancreas some passage of enzymes from the acinar cells, where they are formed, into the blood occurs. This seems to be

due to some degree of "endocrine" secretion of a predominantly exocrine product. This is why pancreatic amylase and lipase are always normally in the blood plasma. There is evidence to indicate that the enzymes reach the blood in this manner rather than by being reabsorbed from the ducts or the intestine after secretion. This implies that small amounts of the enzymes normally leave the end of the acinar cells opposite the gland lumen and traverse the interstitial spaces in going from acini to blood. (14) (16) (23)

Although pronounced elevations of serum enzymes can be produced without histologic evidence of acinar cell damage, the presence of local damage from enzyme action is usually only seen in the presence of necrosis of acinar cells. This suggests that the enzymes in interstitial fluid reach concentrations adequate to produce local damage only when disruption of acinar cells occurs with the release of the contained enzymes into the interstitial space. Once these enzymes reach the interstitial spaces activation of these proteases can occur by a variety of means other than enterokinase. However, it has not been proven that some special factor is not present which produces or accelerates the activation of these enzymes once they enter the interstitial tissues of the pancreas. (23)

Trypsinogen and chymotrypsinogen would be expected to enter the blood the same way as does amylase and lipase. However, their presence has not been demonstrated, but this could be accounted for by the presence of powerful inhibitors of enzymes in the blood

plasma. Moderate amounts of these enzymes can even be tolerated when injected I.V., but large doses produce profound shock and death. (31) (33) (25)

The histopathology seen in acute pancreatitis is one of edema and inflammatory cell infiltration of the interstitial spaces, necrosis and disintegration of acinar cells, intrapancreatic and extrapancreatic fat necrosis and hemorrhage from necrotic vessels, these are in increasing severity of the disease process. All gradations of this process may be seen. While edema, inflammatory cellular infiltration and parenchymal necrosis are common expressions of inflammatory process of all organs, the fat necrosis and the peculiar variety of vascular necrosis with hemorrhage are distinctive and unique features of pancreatitis.

Fat necrosis is caused by the pancreatic lipase acting on the triglyceride of fat containing cells. Thus the neutral fat undergoes enzymatic hydrolysis and the fatty acid released combines with calcium from blood and tissue fluid to form calcium soaps. The replacement of neutral fat by calcium soaps and fatty acid crystals and the associated tissue inflammation produce the characteristic gross and microscopic picture of fat necrosis. Fat necrosis is often seen without hemorrhagic necrosis indicating that the mechanisms protective against digestion of tissue by the proteolytic enzymes is more effective than those acting against lipolysis. Another reason for this could be the fact

that lipase is secreted in the active form by acinar cells. (14) (16) (23)

Hemorrhagic necrosis is produced by the action of the proteolytic enzymes of the pancreas, trypsin and chymotrypsin, on the blood vessel walls, the increased coaguability of blood due to trypsin, and probably also the activity of elastase and collagenase on the blood vessels. In hemorrhagic pancreatitis it is evident that mechanism which prevent activation of the protases before they reach the intestinal lumen are inhibited and that digestion of tissues occurs by the active enzymes. Necrosis of the vessel walls, rupture and hemorrhage is the sequence of events. (16) (23) (31) (33)

These distinctive lesions occur when the pancreatic enzymes in the interstitial spaces exceed a certain level. The lesions may be localized or widespread depending on the quantity and distribution of the activated enzymes. Both, the obstruction and vascular theories can be used to explain much of the histopathology and often some degree of combination of the two seems to fit better yet.

In the presence of obstruction to the outflow of pancreatic secretions from the duct, the passage of the enzymes into the interstitial spaces and consequently into the blood is markedly accelerated. Increase in hydrostatic pressure within the ducts would appear to be the immediate cause of the increased passage of enzymes into the interstitial spaces and the blood. Secretin in the presence of obstruction to the pancreatic duct will cause a rise in serum enzymes even while this pressure is below the

maximum secratory pressure of the pancreas. This indicates that it is the elevation of the intraductal pressure which is the determining factor, but that increased flow of the enzymes can add to the production of pressure as well as produce direct destruction of tissue by their higher concentration in the active form. It is hypothesized that increase of serum enzymes with disruption of acinar cells will allow the pancreatic juices to flow between them in retrograde fashion and thus cause extensive damage. (14) (16)

However, elevations of intraductal pressure too low to produce histologic alterations can produce a marked serum enzyme elevation. This then would appear to be only an accentuation of the normal process of some "endocrine" secretion of these enzymes.

In all species prolonged obstruction of the pancreatic ducts eventually leads to atrophy and destruction of the acinar cells. When the destruction of the acinar cells is very rapid, fat necrosis may occur. This indicates that the determining factor in producing fat and hemorrhagic necrosis is the rate of acinar cell destruction. Vascular necrosis with hemorrhage is seen only with fulminating destruction of the acinar cells. (14) (16)

Throughout the years it has been shown that there are many ways that obstruction of the pancreatic duct occurs in addition to gallstones. Such obstruction can be produced, as previously stated, by many means which usually involve edema and spasm of the papilla of Vater and sphincter of Oddi respectively. How this can

come about can be demonstrated by the use of alcohol. According to Dreiling[14] alcohol acts to produce pancreatitis on a mechanical basis, i.e., the secretion of a stimulated gland against obstruction. Alcohol induced gastric secretions into the duodenum where secretin is produced as a response to this, and through its action on the pancreas incites pancreatic flow. The obstruction to the flow is caused by spasm of the sphincter of Oddi which is an effect of the HCl acid in the duodenum. The edema of the papilla of Vater also adds to the obstruction and this is due to the direct irritation of the mucosa by alcohol. Thus it seems that any cause of edema and sphincter spasm in this region could produce at least some obstruction and any additional stimulation of the gland to secrete could cause acute pancreatitis. However, it is interesting to note that dilatation and thinning of the epithelium of the interlobular ducts, which would be the most distinctive histologic evidence for the existence of obstruction, has been reported in the absence of a definite cause for obstruction only by Carone.[10] So the degree to which obstruction of the ducts occurs in humans is still debatable.

Vascular ischemia of the pancreas has been considered by many physicians to be the major underlying factor responsible for acute pancreatitis and pancreatic necrosis when it is progressive. The exact cause of this ischemia has not been stated, but there are a number of causes listed. Venous thrombosis, ruptured arteriosclerotic vessel, delayed clotting of blood, capillary

thrombosis, the presence of trypsin speeding up blood clotting, accidental ligation of the blood supply to part of the gland, and even bile getting into the parenchyma of the pancreas producing vascular constriction with stagnation of blood flow are among those listed as causing acute pancreatitis. In animals temporary occlusion of the blood supply has created only pancreatic edema while interruption of the blood supply has been shown to create necrotizing pancreatitis.

This indicates that adequate blood flow to the pancreas is important in protecting it from pancreatitis. What seems even more important is the prevention of vascular ischemia in a gland already damaged by some other factor, such as obstruction because the development of vascular ischemia in such a case may easily convert mild edematous pancreatitis to a lethal necrotizing form.

The twofold response of the body to stimuli such as mechanical, thermal or chemical trauma, infectious and emotional factors is well recognized now days. First there is a specific response, such as production of antibodies to infection. Secondly, there is a nonspecific or stressor response whose principal pathways are thought to be mediated through the hypothalamic - pituitary - adrenal axes. (28)

As stated by Hermann (24) about 80 per cent of the pancreatitis cases are secondary or associated conditions, this means that there possibly is some common factor helping to produce the pancreatitis. Selye (43) considered stress as the common factor when

he listed acute pancreatitis as one of the diseases of adaptation to stress. According to Selye, in all diseases there is an endocrinologic derangement, this derangement taking the form of a disproportion between mineralcorticoids and the glucocorticoids, which are antagonists and under normal conditions are in balance. The stress response is mediated by mineralcorticoids causing vascular constriction in the pancreas which may progress to ischemia and thrombosis with tissue necrosis as the end result.

Regardless of the precipitating factor the chain of events caused by stress is seen as first there being a disturbance of the endocrine system which is followed by a liberation of excessive quantities of mineralcorticoids causing vascular spasm in the pancreas, which in turn leads to edema, ischemia and necrosis of pancreatic tissue. The exact physiology involved is not yet clearly understood, but then failure to comprehend the underlying physiologic mechanism of all hormones is regretable, but must be accepted realistically. (28)

Grossman (23) has outlined what he considers to be important factors in pancreatic necrosis and which tend to emphasize obstruction but covering most of the causes.

"A. Factors influencing entry of enzymes into interstitial spaces.

1. Increased intraductal pressure.
2. Disintegration of acinar cells with discharge of the contained enzymes.

B. Factors influencing necrotic potency of juice.

1. Amount of juice entering interstitial spaces
2. Concentration of enzymes in juices
3. State of activation of proteases in juices.

C. Factors influencing the resistance of tissues to the necrotic action of pancreatic juice.

1. Blood supply
2. Damage to tissue by trauma, infection, chemical agents or metabolic dearrangements."

This outline too points out there is likely to be more than one cause in production of acute pancreatitis.

IV. Diagnosis

One of the main reasons for missing the diagnosis of acute pancreatitis in patients with severe abdominal pain is the failure of the physician to consider this diagnosis carefully. The physician will consider biliary colic and coronary occlusion which are much more common, and also consider the possibility of a perforated ulcer, which is about three times as common, but by this time he may not even think of investigating for evidence of acute pancreatitis. Now as acute pancreatitis is more often considered in the diagnosis of an acute abdomen, it is being found to be present more often. Through this careful search many interesting facts about acute pancreatitis are being discovered. A report by Bockus [7] on 94 cases of acute pancreatitis, which will be discussed later, is one of the examples of the interest shown in this disease.

Clinically the patient will experience severe upper abdominal pain of sudden onset. Associated or preceeding feeling of weakness

is not uncommon. The severity of the symptoms will vary directly with the severity of the disease process. Thus the patient may just complain of discomfort or he may be in a state of shock. The pain will usually radiate from the epigastric region to the back, chest, or flank. Nausea and vomiting is commonly present, but associated jaundice is seen in a much smaller percentage. If the diaphragm or peritoneum is involved then limitation of respiratory movement can be seen and in these cases some atelectasis of the base of the left lung may exist. Abdominal distention and paralytic illeus may be present. The temperature, pulse, and blood pressure can vary. Any cutaneous signs such as Cullen's or Gray-Turner's sign are late signs becoming evident from the second to the fourth day and therefore of little help initially. It is because of these indefinite signs and symptoms that the responsibility of the diagnosis of acute pancreatitis also rests heavily on laboratory tests. (1) (7)

Of the laboratory tests the serum amylase determination is the most generally useful procedure in the diagnosis of acute pancreatitis. Even this test is not foolproof because there are other organs in the body producing amylase, for example the salivary glands and the liver. It has only been recently demonstrated that the amylase produced by the pancreas will migrate with and is bound to the gamma globulins as demonstrated by the electrophoretic pattern of serum. It is this gamma globulin bound fraction that is primarily elevated in acute pancreatitis. (12) (25) (33)

The serum amylase is measured in Somogyi units. The range of 60 to 180 units per 100 ml is usually the accepted range of normal values. Its concentration may be increased to more than ten times the normal values in some individuals with acute pancreatitis. It is regarding this elevation range that Knight emphasizes the need to know the normal level of serum amylase of each individual because he has demonstrated that the disease process may be present with an elevation of only 60 units and the total value still falling within the so called "normal" range. This is even more important when one knows that there is no close correlation between the severity of the clinical signs of toxicity and serum amylase values under the present interpretation of them. Routine serum amylase determinations are not done and therefore their normal level in each person is usually not known. This means that when an amylase determination is done during the disease state the value can only be compared and evaluated in respect to the normal range of values, which is quite wide. Depending on this as an index for severity of disease can be misleading in persons having either high or low normal values. A value of 450 Somogyi per 100 cc in a person having a normal value of 150 units would actually be a mild inflammation, but the same value in a person with a normal value of 75 units would indicate a moderately severe disease state of the pancreas. Any reports citing a serum amylase value as being so many times normal means actually that this value is so many times the

maximum normal value for that laboratory. It is because of the variation of normal ranges for some of the laboratories that under the present system of evaluating serum amylase levels one must know the normal values of the particular laboratory that made the determination before any significance can be attributed to their values. (32) (7)

There are also some other disease processes besides pancreatitis that will give elevated serum amylase levels. Carcinoma of the head of the pancreas, peptic ulcer which has penetrated into the pancreas, perforation of an anterior duodenal ulcer, impaired renal function, peritonitis, intestinal obstruction, mumps, salivary gland diseases, some hepatic diseases and opiates have been described as causing elevated amylase values, however, these elevations for the most part have been less than four times the maximum normal value.

Even with all the present inadequacies of this test it is still the best one we have, and when the physician realizes and interprets the amylase values with full knowledge of their limitation, it can be of help in diagnosing and treating acute pancreatitis. The serum amylase will be elevated early in the disease process and it returns to normal within three to four days in uncomplicated cases. It is usually elevated at least five times the normal value. Repeating the test several times within the first fourty-eight hours will help in finding an elevated value as well as giving some idea to the progress of

the initial phase of the disease by knowing approximately what the maximum elevation was. After about four days the amylase value will return to normal regardless of improvement or continuation of the disease. Thus serum amylase is valuable in the diagnosis when it is elevated above five times normal, when it is three to five times the normal it is suggestive of acute pancreatitis, but elevations below this are of no help as a single positive finding.

Other laboratory testing are also of some help, but are less reliable, less constant or harder to do than the serum amylase. Peritoneal fluid amylase is consistently higher than the serum amylase and it will also stay elevated two to four days longer. The urine amylase remains elevated longer than serum, but is less reliable when glycosuria is present.

According to Street the Somogyi technique is subject to a potential error in which results vary with blood-sugar levels. Street and Close have described a method of determining serum amylase levels using amylose as a substrate. Rifkind states this method is rapid, simple and reproducable and is not subject to variations with blood-sugar levels. The normal range if from 6 to 33 Street-Close (s.c.) units.(38)

Serum lipase levels of blood can also be determined. The lipase will be elevated with the same frequency and due to the same causes as will the amylase, but it will stay elevated longer, ten to fourteen days. The normal range is up to 1.5 units/cc (N/20 NaOH). Blood lipase has not been studied as thoroughly as

the amylase, the technique is less standardized and therefore of less help in diagnosis. The blood level of lipase is supposed to fluctuate less than the amylase level, but with the use of opiates one may see a tremendous increase, up to twenty times normal.

Low serum Ca^{++} levels may be seen with severe acute hemorrhagic pancreatitis, even to the degree of tetany, However, this is found only between the third and fourteenth day. (33)

At the present time there is no way to determine trypsin blood levels. A rather new test used in acute pancreatitis is determining the antithrombin titer of plasma. An elevation in this titer has been found, in acute pancreatitis and in some cases of chronic recurrent pancreatitis, but the level remains normal in acute surgical abdomen. This test has less false positives and could be used as a supplementary test confirming borderline values. This technique will have to be studied more thoroughly before its full value is known. (12) (25) (33)

Some other helpful points in diagnosis were brought out by Bockus (7) in his analysis of 94 attacks of acute pancreatitis in 78 patients. Eighty-six per cent of the patients had also either biliary tract disease or a history of excessive alcohol intake. The admission diagnosis was correct in 57 per cent of cases. Biliary tract disease was the most common wrong diagnosis. The younger age group was associated more with alcohol. Ma

Male patients were predominate in number.

Pain was the major complaint in 98 per cent of the cases. Some abdominal finding was present in 92 per cent, most common finding was direct tenderness in 87 per cent. The median temperature was 100.5° F. Chest rales were present in 30 per cent. In alcoholics the rales were on the left side, in patients with biliary tract disease on the right side. Leukocyte counts ranged to 30,000. In the alcoholic group 2/3 were below 10,000. Icterus was present in half of the patients admitted with biliary tract disease.

The serum amylase was more than five times the normal value in about half of the patients. Eleven had normal amylase levels, but of these nine had elevated serum lipase. In all the patients with a 900 mg. per cent or higher value the temperature was at least 101° F. and the WBC at least 15,000. In 29 per cent of the patients the amylase values remained elevated from ten to thirty-nine days. In about 3/4 of these patients a complication was later proven to be present.

Serum lipase was normal in 13 patients, but 11 of these had elevated amylase levels. In only about 1/4 of the cases was the lipase more than five times normal.

The initial EKG and flat film of the abdomen were of very little diagnostic help. Both of these procedures should be done, if for no other reason than, to eliminate or confirm some other disease process.

Bockus noted that the disease state in general was more severe in the alcoholics than in the group with associated biliary tract disease.

V. Steroids as a Cause of Pancreatitis

For many years acute pancreatitis was considered to be a surgical emergency. During the years the conservative medical management of these patients has gained acceptance because of the better results that were obtained. Even with this treatment there still exists a mortality of around 10 per cent in the more severe cases. (26) (29)

The conservative approach consists of: (1) controlling the pain, (2) reducing the spasm of sphincter of Oddi, (3) decreasing the pancreatic secratory activity, (4) maintaining fluid and electrolyte balance, (5) preventing shock, and (6) preventing infection. Gradually it was realized that even with this management it was not always possible to prevent the development of progression of an acute pancreatic process. Some physicians felt that despite the imperfect knowledge of the cause or causes of pancreatitis enough is known of the clinical circumstances of this baffling disease to warrant more aggressive treatment than has heretofore been practiced. This form of more aggressive treatment has been expressed by the use of glucocorticoid steroids and ACTH in cases of acute pancreatitis. Since Stephenson first reported successful treatment of a patient with acute pancreatitis with cortisone much controversy has existed regarding its usage

in this disease. This controversy has been continuing because there are reports in the literature of patients, who have been on steroids, developing changes in the pancreas which are histologically compatible with changes seen in acute pancreatitis. Some of these patients have also been reported to have had symptoms compatible with acute pancreatitis. At the present much of the reasoning against the use of steroids in acute pancreatitis is based on experimental evidence from animals treated with steroids and the comparison of the pathologic changes developed in them with those seen in humans who have been on steroids. (7) (29) (45)

The mechanism by which steroids induce pancreatitis is unknown, but there are a number of hypotheses, Stumpf (46) has shown that in cortisone treated rabbits the serum lipids, primarily the neutral fats, became markedly elevated. This elevation in lipids tended to occur before there was an elevation of the serum amylase in these rabbits. Rich (37) has also demonstrated this rise in serum lipids. Stumpf suggested on this basis that since pancreatitis is seen in man in association with hyperlipemia the possibility of steroids producing hyperlipemia, which in turn induces pancreatitis must be considered. This is not the cause according to Nelp (35) and Carone (10) who states that the serum neutral fats fall after continued administration of cortisone. Bencosme (5) has considered these lesions to be obstructive and possibly caused by the cortisone induced changes in the viscosity of the secretions. However, Dreiling (13) has shown that in man

following ACTH and cortisone administration there is a significant depression in the exocrine pancreatic secretions. Carone[10] reports that others have suggested that steroids may produce a less soluble lipid or larger lipid particles, and that these altered serum lipids might produce fat embolisms and thus produce pancreatic lesions. However, Carone [10] was unable to demonstrate any significant fat embolisms in fat stained sections in his autopsy series.

The actual pathological changes in the pancreas of steroid treated animals and humans indicates that there is a scattered obstruction of the excratory passages. Inspissated secretions are frequently seen in the collecting ducts and/or the acinar spaces. Acinar dilation is a constant finding. Similar changes have also been observed in uremia, high intestinal obstruction, ulcerative colitis and severe infection. [35]

The incidence of acute pancreatitis in the population receiving steroids has not been studied. Even though it appears to be quite low it is probably higher than generally appreciated. There are probably three reasons for this: (1) there is a lack of recognition that pancreatitis is a possible complication of steroid therapy, (2) any epigastric pain occuring during steroid therapy is most often associated with a peptic ulcer, and (3) steroids may easily mask the symptoms of the pancreatitis. The following are some of the reports on supposed

steroid induced acute pancreatitis. (35)

Carone and Liebow (10) studied the incidence and the nature of pancreatic lesions in 54 patients who were receiving corticotropin or adrenal steroids at the time of death. Sixteen of the fifty-four patients had either focal pancreatitis, fat necrosis or both. Only 2 of 54 in a comparable control group had focal pancreatitis. On histologic examination the pancreatitis was interstitial with slight edema and collection of leukocytes. These changes were diffuse in some parts, but other large parts of the parenchyma were uninvolved. The acinar changes consisted of focal dilatation of clusters of acini, with a variable degree of flattening of the lining cells. Often the cells in the dilated acini were so markedly flattened that they created the appearance of dilated ductules. The lumena of the dilated acini usually contained amorphous, pink staining substance suggestive of inspissated secretions.

There were also some interesting additional facts about these cases. In 15 of the 16 cases with pancreative changes there were severe acute infections. Bacteremias were present in 4, in the other eleven no blood cultures were done. Infections have been shown to cause pancreatitis. None of these 16 patients had any signs or symptoms of pancreatitis. There is no laboratory data in regards to pancreatitis in these cases.

The authors consider the lack of hemorrhage to suggest that the pancreatitis was not severe enough to cause digestive necrosis

of the walls of the vessels by released pancreatic ferments, and that these steroid induced changes in the pancreas are not necessarily progressive, but may subside and heal. They also recognize that very large doses of these hormones can be tolerated over long intervals without the development of acute pancreatitis or fat necrosis.

Nelp [35] reported on six patients in whom acute pancreatitis was induced; one had an attack while being on a continuous dose, two had the attacks when their doses were reduced and the last one experienced an attack one day after his steroids were discontinued. The diagnoses were made at surgery or autopsy in five of the six cases. The other case was diagnosed clinically. The diseases that they were being treated for were chronic ones and there is no proof that the steroids pancreatitis contributed in their deaths.

Inspissated secretions were found in the ducts in each case autopsied at the time of acute pancreatitis, cases 3, 4, and 6. The other case, case 5, autopsied 2 years after the one bout of acute pancreatitis showed focal areas of destroyed acinar tissue replaced by dense scar. In these areas the islet cells were preserved. This suggests that the original lesion obstructed the ducts of the involved segments. Focal acinar dilatation was also prominent in two of the autopsied cases. Nelp feels that prolonged or high dose steroids therapy favors the development of pancreatitis rather than causing it.

Rifkind [38] studied the serum amylase levels in patients during steroid therapy. He had a good range of subjects going from some who had only been on steroids for a few days to one man who had had 200 to 600 mg. of cortisone per day for about six years. He compared their values with a control group. He found a statistically significant rise in the steroid group, but it was so slight that he had doubt whether pancreatic lesions could be responsible for this difference. This also showed that the frequency and extent of the rise of serum amylase noted by Stumpf [46] in the cortisone rabbits is not equaled by man with the usual doses of steroids. In rabbits the daily dose was 3 to 8 mg. per kg. body weight for twenty-one to eighty-one days. In man equivalent doses are seldom prescribed.

Baar [2] reported two cases of severe pancreatic necrosis in children treated over a prolonged period of time. In both of the cases the pancreatic tissues showed necrosis, areas of hemorrhage, and marked destruction of the acinar cells. He felt that the pancreatic lesions were probably steroid induced because pancreatitis as such is very rare in children.

Robowska [39] reported a case of fat necrosis and hemorrhage of the pancreas in a young boy who was treated with varying doses of corticotropin over a four month period for Still's disease. The author is not certain that these lesions were steroid induced because the same lesions could have been caused by Still's disease, by the pneumonia or smallpox that the boy had.

Bourne (8) reports a case of acute pancreatitis occuring in a man being treated for nephritis. The diagnoses was made by marked (more than 5 times normal) serum amylase elevation. The prednisolone was not discontinued till two months later. The author feels that pancreatitis can occur during steroid therapy, but that this is probably a rare occurance. They did not feel the pancreatitis was an indication for stopping the steroids in this case.

Oppenheimer (36) reported an increased incidence in acute pancreatitis in children treated with steroids or ACTH for renal disease or leukemia. In the renal disease group three children on steroids died from acute pancreatitis while another seven had lesions suggestive of acute pancreatitis. Thus lesions were found in 10 out of 25 patients. The control group had 4 cases of chronic pancreatitis in 27 patients. In the leukemia group the control group did not have any acute pancreatitis, while the steroid group had 4 from a group or 25 patients. These children in the steroid group had been receiving steroids anywhere from three weeks to several years. The dosages of the steroids however is not reported. The pathological lesions were for the most part focal dilatation of ductules and acini with fat necrosis in some cases.

Zion (47) reports a case of scleroderma being treated with cortisone and corticotrophin over a fourteen month period, continuously on high dosages the last 5½ months of her life, who

at the time of autopsy had an acute superimposed on chronic, pancreatitis. However, the author feels that during treatment the patient developed a fatal illness which was thought not to be directly related to the scleroderma or the therapy.

The duration of treatment and the total amount of steroids and corticotropin received by these patients will be summarized later in a chart.

The cases reported here by the authors vary greatly in the severity of the disease. With the exception of the three deaths due to pancreatitis reported by Oppenheimer [36] and the two severe cases reported by Baar, [2] the rest of the pancreatic changes reported were mild and focal. It now becomes a question of how much importance should be placed on the deaths of the three children with renal disease. It is well known that in renal disease the excretion of pancreatic enzymes is decreased and that the increased level of enzymes plus the obstruction of the ducts could have caused the damage seen. None of the authors feels certain enough to state that the damage seen in the pancreas due to steroids is severe enough to keep him from using them in other cases when it is indicated. The one thing that stands out is that many of the patients showed evidence of damage to the pancreas only after a long time on steroids and after they had gotten a large total amount of steroids. However, there have been enough reports after only several days on steroids to make one think of the possibility of acute pancreatitis in any of these

patients who develop sudden abdominal pain, while on steroids.

VI. Treatment of Acute Pancreatitis with Steroids

Since Stephenson's [45] initial report in 1952 on a case of acute pancreatitis treated successfully with steroids, there have been many enthusiastic supporters for this form of treatment. Most of these favorable reports were on patients who before the beginning of steroid therapy were thought to be dying. The responses were dramatic and in the minds of those physicians, lives were saved. The dosage given, the total amounts given, and the duration of therapy varied markedly. Very little new information regarding dosage has been added in the past years. The main problem in this is the difficulty in applying a double blind study or a controlled study using steroids in acute pancreatitis because of the unpredictable course of this disease. Those physicians using steroids admit that they are doing so on an empirical basis rather than scientific bases, but since they feel that they have saved lives this way, they are willing to continue using steroids when they feel they are indicated. At the present time Kaplan is making a five-year survey of acute pancreatitis at the Touro Infirmary in New Orleans, and since he is one of the main proponents for this form of treatment, his report will undoubtedly add to the present knowledge of this form of treatment of acute pancreatitis.

Stephenson [45] reported that he used 100 mg. of cortisone acetate I. M. x 3 doses at a point in the patient's disease when

severe shock was present and death appeared to be imminent. The blood pressure was obtained for the first time in this patient 8 hours after the original dose of 100 mg. of cortisone. Laparotomy was done the following day, for a possible ruptured gallbladder, at which time diagnosis of acute hemorrhagic pancreatitis was made. Stephenson felt that the recovery of the patient was influenced favorably by the cortisone.

Eskwith [20] was the next to report what he felt was a case in which steroids had proben to be beneficial. He started the patient on 300 mg. of cortisone daily after the patient had been in the hospital for five days with severe epigastric pain which had failed to respond to the usual medical therapy for acute hemorrhagic pancreatitis, which was diagnosed by laboratory studies and physical findings. This dosage was gradually decreased over the next eight days while the patient showed marked symptomatic improvement. On the eighth day of therapy with steroids the patient developed increased abdominal pain and an elevated temperature. At this time the dose of cortisone was increased to 300 mg. per day. The patient was kept on this dosage till she was dismissed seven days later free of symptoms.

He states that the cortisone was started on an empirical bases with the hope that this might lessen the pathologic reaction and/or give symptomatic relief. He states that the patient's improvement was remarkable when judged by general appearance, relief of pain and an increased appetite. He did find that the

patient's serum amylase remained elevated for another two and a half months, but during this time she did not have any symptoms.

Brockis [9] reported two cases of acute pancreatitis in whom cortisone was used to prevent and treat circulatory collapse because a number of patients with this disease will pass into a state of peripheral circulatory failure from which they do not recover. The first patient was started on 300 mg. cortisone a day after the patient had had acute pancreatitis for seven days and her condition had worsened to the point where she was close to being in shock. Her condition gradually improved and the cortisone was reduced respectively. Brockis also found it difficult to take her off the cortisone after an abscess in her left lumbar region had been incised and drained because there was a general relapse in her condition. After about fourty days the steroids were discontinued. During the next six months she still had occasional abdominal symptoms. The second patient was started on 300 mg. of cortisone after having had acute pancreatitis for less than two days. Within fourty-eight hours after starting this treatment there was marked symptomatic relief. The dosage was gradually decreased after the third day and the cortisone was discontinued on the fourteenth day. No history of any further complications.

Brockis felt that the rapid improvement in the general condition and the relief of the pain which began after the administration of the cortisone were impressive. An indication that

the cortisone had aided recovery was shown in the first patient by the relapse which occurred when the drug was stopped on the twentieth day and the prompt improvement as soon as cortisone was restarted. He feels that the place of cortisone lies in the control of the severe attack of this disease when there is evidence of profound circulatory disturbance, and that its administration should be stopped at the earliest possible moment.

Bloodsworth [6] treated a case of acute pancreatitis associated with mumps epidemic parotitis with cortisone the following way. The patient received 100 mg. cortisone, followed by 50 mg. every six hours for three days which in turn was followed by 50 mg. cortisone every eight hours for three days. He felt that the cortisone reverted a downhill course to one of recovery.

Jones, [26] in considering medical management of acute pancreatitis, states that he knows that cortisone acetate I. M. has been useful in certain instances and when the need is urgent hydrocortisone (Cortef), 100 mg. diluted in isotonic saline may be given I. V. This latter method has seemed to him to be life saving in two personally observed instances.

Bartholomew [4] feels that in most cases the disease is self-limiting, but that the use of ACTH and cortisone in acute fulminating pancreatitis especially following abdominal exploration, has been life saving. However, he reminds us that it is the custom to publish only the successful results.

Rogers [40] has also reported a series of six acute pancreatitis

cases treated with steroids. His experience has been that at times the difficulty in diagnosis of an acute abdomen leaves no other recourse than surgery by which the presence of hemorrhagic and necrotic pancreatitis may be confirmed and other conditions correctable by surgery excluded. Three of the following cases were of such nature. In the first case a laparotomy was done at which time a moderately severe edematous pancreatitis was found to be present. He received immediately 15 mg. of hydrocortisone followed by 25 mg. prednisone a day for five days. Then the prednisone was decreased over the next eleven days and the patient was dismissed having received a total of 15 mg. hydrocortisone and 260 mg. prednisone. A laparotomy was also done on the second patient and a severe hemorrhagic pancreatitis, which was expected to be fatal, was discovered. Hydrocortisone 50 mg. stat was given. This was followed by 20 mg. prednisone per day. The prednisone was gradually reduced over the next thirty days when the patient was dismissed on 5 mg. prednisone daily for the next fourteen days. There were no complications. The third case was similar to the previous one. Here, too, a laparotomy was done on a gravely ill patient in whom a necrotic pancreas was found to be present. He received 50 mg. hydrocortisone then, and this was followed by 25 mg. of prednisone per day for two weeks when the dose was decreased gradually over the next sixteen days. He received a total of 500 mg. prednisone. In the other three cases the diagnosis was made without surgery. The treatment in these cases was similar.

Prednisone 25 mg. per day was given and this dose was decreased gradually till it was discontinued after one to two weeks therapy. Rogers felt that at least two of the patients, cases two and three, were likely to die and that a rapid improvement dated from the administration of cortisone. He also felt that the other four cases would have probably recovered without any steroids. The rate of recovery appeared to be favorably influenced by the cortisone, and this method of treatment should be considered as a potentially beneficial therapy for a condition which can be refractory to any treatment and which is often fatal.

Solem (44) reports a case treated successfully with ACTH. The patient was kept on 100 mg. ACTH for three days at which time the drug was discontinued. A mild relapse occured which required another three days of 100 mg. ACTH per day before she became and remained asymptomatic. This patient responded abruptly and favorably to the administration of ACTH.

Ericson (19') reports that he has treated successfully seven acute postoperative pancreatitis with a long-acting ACTH preparation intramuscularly. He used 100 I. U. a day for several days till the patient was symptom free. He reports that since 1955 he has always used a long-acting preparation of ACTH as an adjunctive in 60 cases treated. Only one patient out of this group died. That patient died from anuria after laparotomy. All the other patients recovered rapidly. Based on his experience he recommends ACTH as an adjunctive treatment of acute pancreatitis,

and suggests that long-acting preparations and big dosages should be used. In cases of emergency the ACTH can be given intravenously.

Anderson (1') also reported having treated two postoperative pancreatitis cases with hydrocortisone and cortisone. He started out by giving 200 mg. hydrocortisone intravenously the first day and using cortisone 50 mg. intramuscularly every six hours thereafter; the cortisone dosage was reduced gradually as the patients became symptom free. To test the possible favorable effects of adrenocorticosteroids they induced pancreatitis in dogs. In these dogs, with a form of acute pancreatitis quite similar to that noted in humans, adrencorticosteroids when given alone, effected a definite reduction in mortality and improvement in clinical course. However, similar improvement was seen when antibiotics alone were used. The best results were obtained in the group of dogs which was treated with antibiotics and adrenocorticosteroids. These experimental findings suggest that adrenocorticosteroids are worthy of further trial as an adjunct in the treatment of human pancreatitis. TP Kaplan,(29) himself, has reported using steroids to treat acute pancreatitis in twelve cases. He has used the theory of stress, with the development of an imbalance between mineralcorticoids and glucocorticoids, as the rationale of his use of cortisone in this disease. The main deficiency in the use of cortisone is the lack of any means, at the present, of estimating the effective dosage

steroids in the individual case. He uses the following criteria in determining when to start steroids:

> "1. Acute hemorrhagic pancreatitis, diagnosed at surgery
> 2. Acute hemorrhagic pancreatitis, diagnosed medically, showing rapid progression, with evidence of shock or overwhelming toxemia; or failing to evidence improvement within 72 hours of the onset of treatment."

His routine is to give 300 mg. of hydrocortisone or its equipotent analog for the first few days. This is gradually reduced and discontinued in ten to fourteen days. In very severe cases one should not hesitate in using a dose as high as 500 mg. of cortisol, or its equivalent analog, intravenously every six hours for the first one or two days. The addition of cortisone to the therapeutic drugs should give the surgeon more courage to explore the abdomen in cases when the diagnosis seems to be pancreatitis, but because of diagnostic limitations he cannot be sure. This would prevent the over-looking of such abdominal catastrophes as require surgery, including, mesenteric thrombosis, intestinal obstruction or rupture of some viscus. The use of cortisone will counteract the primary stressor agent as well as enable the patient to tolerate the added insult of surgery. Kaplan probably summarizes the feeling of those physicians using steroids with this statement, "The rationale for the use of cortisone in acute pancreatitis is, of course, debatable. The proof of its value, however, is the survival of patients who otherwise would surely have died."

So far all the reports have shown the supposed effectiveness

of cortisone and ACTH to help reverse a severe state of the disease, but nothing has been said about its use in the milder stages. The Gentrys,[32] for one, have used a modified version of Kaplan's suggested dosages for other degrees of the disease than only the acute hemorrhagic type. The following case history should show the flexibility they use in treating this disease process.

A thirty-six year old white male on 3-27-56 became suddenly ill, with severe abdominal pain and vomiting. Physical exam revealed a rigid abdomen, tenderness in region of umbili us, with some pain radiating to the back. Bowel sounds were normal. History was noncontributory. Laboratory results showed: Blood, RBC - 5.42 mill., WBC - 11,900, Hgb. - 16.0 gm. Serum amylase = 300 Somogyi units. (Normal limit to 150 units). X-ray - flat film of abdomen showed local ileus in region of the small intestine which is compatible with acute pancreatitis. Diagnosis of acute pancreatitis was made and therapy was started. Patient was given intravenous fluids with vitamins. Demerol® 75 mgm. was administered. 100 mg. Solucortef® was given in 1000 cc N saline. On 3-28-56 patient was somewhat better. The abdomen was softer and there was less pain. Intravenous fluids were discontinued, and Prednisolone, 5 mg. q.i.d. started.

After this the patient showed continuous improvement. On 3-3-56 the serum amylase is 125 units. The prednisolone was

gradually diminished. On 4-2-56 he was up and about, four days later he was dismissed. Later they felt that perhaps a larger initial dose of Solucortef® would have speeded up the patient's recovery.

During the past seven years they have had better results in treating mild and severe cases of acute pancreatitis by using cortisone than they had earlier when all they used was the standard medical regimen. They have found that using the cortisone early in the disease will decrease the pain markedly and the patient will look and feel better. Through this form of treatment they are able to, most of the time, avoid the use of naso-gastric suction, which by itself adds greatly to the patients discomfort, and prolonged use of intravenous fluid therapy.

However, they emphasized that cortisone is not a panacea in the treatment of acute pancreatitis, but that avoiding its use in diagnosed cases of acute pancreatitis adds an unnecessary burden to an already severely ill patient.

VII. Summary and Conclusion

Since the original description by Opie in 1901 on the etiology of acute pancreatitis when he described a case of acute hemorrhagic pancreatitis due to a stone impacted at the ampulla of Vater, great effort has been made by pancreatic physiologists to construct a unified concept of the pathogenesis of inflammation within the pancreas. So far no universally acceptable explanation for the pathogenesis of this disease has been found.

At first obstruction to the outflow of pancreatic secretions was thought to be the cause. Later the vascular concept of this disease was introduced, and since the work of Selye and Kaplan this theory has gained much support.

It has become evident that the initial phase can be produced by many causes, but that in the severe forms of pancreatitis one sees a combination of both the obstructive and the vascular phase of this disease process. It is often impossible to state which of the two came first since either cause may produce the other. However, in the most severe cases, acute hemorrhagic pancreatitis, one always sees the involvement of blood vessels of this gland.

In the diagnosis of this disease one has to use a combination of clinical and laboratory evidence to try and differentiate this disease from the acute surgical abdomen. At times this is impossible and a laparotomy has to be performed.

For many years acute pancreatitis was considered to be a surgical emergency. During the years medical management of these patients has become the accepted form of treatment. Even with the improvements in the medical management the mortality in the more severe cases still remained around 10 per cent.

The addition of steroids to the medical management of this disease has brought forth a series of reports showing that steroids are capable of producing lesions in the pancreas which

are consistent with lesions seen in acute pancreatitis. Most of the reports indicate that the lesions seen are focal and that in general quite minimal damage is seen in the pancreas. The exceptions to these reports were those of Baar and Oppenheimer. Baar reported two cases where hemorrhage and necrosis of the pancreas was present. Oppenheimer reported three cases of death, in a group of children with renal disease, from acute pancreatitis which were thought to be steroid induced. However, none of the authors states that they recommend the discontinuation of steroid therapy for a disease on the basis of present day knowledge.

Those physicians that have treated acute pancreatitis successfully with steroids are found to be strongly in favor of this method of treatment. Such words as "dramatic," "spectacular," and "life-saving" are often found in their reports on these cases. So far most of them have limited the use of steroids to the severe cases where they have been afraid the disease process would not be reversible. Most prefer cortisone or hydrocortisone for this, but some have gotten good results with ACTH. They have used these drugs on the basis that these agents surpress progressive cellular damage and interrupt the chain reaction that follows and progresses after the initial inflammatory stimulus. The other beneficial action seems to be a non-specific antitoxic and antishock effect produced by the adrenal corticoids. Some have used cortisone also to prevent the milder forms from progressing to the more severe types, and in their opinion also this form of treatment has been most beneficial to the patient.

The present day evidence indicates that the glucocorticoids are beneficial in the severe stages of the disease, and that in the milder forms the course of the disease may be shortened and the progression of the disease halted. The fear of glucocorticoids causing pancreatic damage does not seem to be at the present a reason for not using them because the damage they produce is generally mild while their beneficial action can be life saving. It has been noted before that some diseases are caused by the same drugs that cure the diseases. In this case the disease is worse than the risk taken in curing it.

Acute Pancreatitis Cases Reported Caused by Steroids

AUTHOR		STEROID GIVEN	TOTAL DOSAGE IN UNITS OR MG.	DAYS OF TX.
Carone	1.	Cortisone	1150	9
	2.	Cortisone	1500	3
	3.	Cortisone	10725	30
	4.	Cortisone	1300	7
	5	ACTH	5570	78
	6.	ACTH	240	6
	7.	Cortisone	?	2 years
		ACTH		
	8.	ACTH	800	8
	9.	ACTH	200	3
		Cortisone	200	
	10.	ACTH	200	3
		Hydrocortisone	300	
	11.	Cortisone	1000	6
		Hydrocortisone	300	
	12.	Hydrocortisone	300	3
	13.	Cortisone	8900	120
		ACTH	1760	
	14.	Hydrocortisone	325	4
	15.	ACTH	80	7
	16.	DOCA	270	240
		Cortisone	2900	
		Hydrocortisone	1625	
Nelp*	1.		2500	45
	2.		8900	400
	3.		735	27
	4.		3840	70
	5.		?	3½ years
	66.		5000	
Baar	1.		?	120
	2.	Cortisone	23000	300
Robowska	1.	ACTH	3700	120
Bourne	1.	Prednisone	390	44
Oppenheimer	3 cases	ACTH or Cortisone	?	21 days -- 3 years
Zion		Cortisone	16875	165
		ACTH	1520	24

*Nelp. Doses given are in units having the following value:

1 unit= 1 mg. prednisone
1 unit= 5 mg. cortisone
1 unit= 4 mg. hydrocortisone
1 unit= 1 unit ACTH

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