DATA CONCERNING THE ETIOLOGY AND PATHOLOGY OF HEMORRHAGIC NECROSIS OF THE PANCREAS (ACUTE HEMORRHAGIC PANCREATITIS).[1]

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Hemorrhagic pancreatitis was clearly recognized about fifty years ago by Klebs,[2] who believed that the eroding action of the ferments formed by the pancreas was responsible for its occurrence. The classification of acute pancreatitis almost universally adopted, and knowledge of the symptomatology of the various types of inflammation date from the Middleton-Goldsmith lecture of Fitz,[3] delivered before the New York Pathological Society twenty years ago. A certain medico-legal importance has been attached to a disease which may be a cause of sudden unexplained death, but it is perhaps noteworthy that some writers who have emphasized this view have described as hemorrhagic pancreatitis the relatively common post-mortem autolysis which occurs in the pancreas. The cause of the lesion has remained obscure until comparatively recent studies have shown that it can be readily reproduced in lower animals by a variety of means. Human cases have been carefully studied with the aid of these experimental data, with the purpose of defining the cause of the lesion.

It is probable that the physiologist, Claude Bernard,[4] produced the lesion, though he failed to recognize it, years before it had been described in man. It is noteworthy that he injected into the pancreatic duct that fluid, namely, bile, which, as subsequent observations have shown, may cause the lesion in man. In his lectures on experimental physiology, published in 1856, Claude Bernard describes the injection of a mixture of bile and sweet oil into the

[1] Received for publication April 20, 1909.

[2] Handbuch der pathologischen Anatomie, Berlin, 1868, i, 556.

[3] *Med. Rec.*, 1889, xxxv, 197, 225, 253.

[4] Leçons de physiologie expérimentale, Paris, 1856, ii, 278.

pancreatic duct of the dog; the animal died after eighteen hours; there was intense peritonitis and the pancreas was red and contained numerous ecchymoses. Subsequent observers have shown that acute hemorrhagic pancreatitis accompanied by disseminated necrosis of fat can be reproduced by similar injection of a variety of substances. The list of substances which have been successfully employed is long, and suggests the possibility that mechanical injury of injection is sufficient; neverthless, numerous control experiments have demonstrated that various bland substances fail to cause the lesion.

Hlava[5] (1890) first showed that typical acute hemorrhagic pancreatitis with foci of fat necrosis disseminated in the abdominal fat, can be produced in animals by injecting gastric juice through the opened duodenum into the pancreatic duct. Bile (Opie)[6] injected into the duct causes the change; the bile salts (Flexner)[7] are effective, but other constituents of bile fail to produce it. Duodenal contents have been subsequently employed with the same result (Polya).[8] The lesion may be produced with weak solutions of a variety of acids including hydrochloric, nitric and chromic acids, and an alkali, sodium hydroxide, has the same effect (Flexner)[9]; injection of formalin causes the lesion. Sweet oil has the same effect; fatty acids and sodium soaps of these acids have been successfully used, but glycerin is ineffective (Hess).[10] It is difficult to define any common character of these substances, save their power to injure the tissue with which they come into contact. A variety of bland substances have been tested with negative result; these include blood, blood serum (Flexner and Pearce);[11] agar-agar (Flexner), paraffin (Thiroloix,[12] Hess), emulsion of starch (Hess), etc.

[5] *Bull. internat. de l'acad. des sciences de Bohême,* 1898; and *Arch. Bohême,* 1890, iv, 139. Cited by Katz and Winkler, *Arch. f. Verdanungskr.,* 1896, iv, 289.

[6] *Bull. of the Johns Hopkins Hospital,* 1901, xii, 182.

[7] *Jour. of Exper. Med.,* 1906, viii, 167.

[8] *Berl. klin. Wchnschr.,* 1906, xliii, 1562.

[9] Contributions to the Science of Medicine. Dedicated to William H. Welch. *Johns Hopkins Hospital Reports,* 1900, ix, 743.

[10] *München. med. Wchnschr.,* 1903, 1, 1905.

[11] *Univ. of Pennsylvania Med. Bull.,* 1901, xiv, 193.

[12] Thesis, Paris, 1892.

Especially significant is the fact that acute hemorrhagic pancreatitis produced by the methods which have been described, may be wholly unaccompanied by bacterial infection. Injection of cultures of various bacteria in small amount causes suppurative or chronic interstitial inflammation (Carnot[13] and others). Introduction of fluid cultures in considerable amount into the pancreatic duct may cause the hemorrhagic lesion which is perhaps referable, according to Hlava, to the acid products which they may contain.

Acute hemorrhagic pancreatitis in man has followed various injuries to the gland; fatal hemorrhagic or gangrenous pancreatitis it is well-known has followed immediately localized injury in the epigastrium, the kick of a horse, crushing of the body between the bumpers of two cars, passage of the wheel of a wagon over the body, etc., and in a few instances hemorrhagic pancreatitis with fat necrosis has occurred about the tract of a gunshot wound of the pancreas. Experimental studies have not fully explained such occurrences. A series of ligatures about the gland occluding both blood vessels and ducts causes a similar lesion, usually fatal within twenty-four hours (Katz and Winkler)[14] (Doberaurer)[15]. Injection of various substances which may act as emboli such as air, oil, paraffin (Bunge),[16] into the arteries of the gland cause necrosis of pancreatic parenchyma and of neighboring fat. Simple experimental crushing of the pancreas does not cause the lesion, but crushing associated with ligation of the blood vessels causes a hemorrhagic lesion accompanied by fat necrosis (Levin).[17]

Before attempting to show how these experiments explain the etiology of acute hemorrhagic pancreatitis in man, we wish to point out certain characters common both to the human and to the experimental lesions. Recognition of these peculiarities is essential to a clear understanding of the lesion, but they have not received the attention they deserve. Hemorrhage into the pancreas, believed to have much analogy to cerebral hemorrhage and caused perhaps by weakness or disease of the blood vessels of the gland, has often

[13] Thesis, Paris, 1898.
[14] *Arch. f. Verdanungskr.*, 1896, iv, 289.
[15] *Beitr. z. klin. Chir.*, 1906, xlviii, 456.
[16] *Arch. f. klin. Chir.*, 1903, lxxi, 726.
[17] *Jour. Med. Research*, 1907, xvi, 419.

been designated pancreatic apoplexy. There has been much discussion concerning the relation of hemorrhage and inflammation. Does inflammation occur as a consequence of hemorrhage, perhaps as the result of infection of hemorrhagic tissue, or is hemorrhage the result of severe inflammatory change? Study of the experimental lesion confirmed by the examination of human cases has rendered this discussion unnecessary, for it has shown that both hemorrhage and inflammation are secondary to necrosis of pancreatic parenchyma. The first effect of bile or other substance which causes the lesion, is death of pancreatic tissue with which the irritant comes in contact. Experiments of Flexner and Pearce have demonstrated the surprising rapidity with which this change occurs; one hour after injection of an irritant into the duct of the gland, hyaline necrosis has occurred and inflammatory products have found their way into the necrotic area. Such facts explain the sudden onset of the disease. One of us[18] has described the necrosis caused by injection of bile into the pancreatic duct of an animal, and has found that it affects not only the pancreatic cells, but the interstitial tissue of the gland together with the blood vessels which it contains. Necrosis of the walls of blood vessels explains the multiple hemorrhages which characterize the lesion. Inflammatory changes, moreover, occur only at the margin of the necrotic tissue. These observations show that the essential feature of the lesion is neither hemorrhage nor inflammation, but consists in death of large masses of pancreatic tissue. They emphasize the fact that acute hemorrhagic pancreatitis is not a bacterial infection like pancreatic abscess, but is primarily necrosis of the pancreas usually caused by contact of some irritant substance with the cells of the gland.

The fact that necrosis in mass is the essential feature of the lesion is well illustrated by Case II (p. 571) which is a typical instance of acute pancreatic necrosis accompanied by disseminated focal fat necrosis. This case is noteworthy because macroscopic hemorrhage is almost wholly wanting although the pancreatic parenchyma has undergone almost complete necrosis; a few black spots represent changed blood but there is no diffuse hemorrhagic infiltration of the necrotic tissue.

[18] *Bull. of the Johns Hopkins Hospital,* 1901, xii, 182.

The lesion usually described as acute hemorrhagic pancreatitis has not the characters of an inflammatory process. Widespread necrosis of pancreatic parenchyma is primary and such inflammatory changes as occur are found only at the margin of the necrotic tissue. A clearer understanding of the nature of the disease would doubtless result if the term hemorrhagic necrosis of the pancreas were used in place of acute hemorrhagic pancreatitis.

Similar lesions do not occur in other organs save, perhaps, in the stomach, where impaired vitality of the mucosa is followed by necrosis and subsequent ulceration, often with hemorrhage brought about by action of the gastric juice upon the injured tissue. The analogy is significant for the pancreas too contains an active proteolytic enzyme which unrestrained is capable of destroying tissue. The peculiar necrosis which affects the pancreatic parenchyma is doubtless referable to the trypsin which is contained in the pancreatic cells. Numerous studies have clearly demonstrated that the necrosis of fat which accompanies hemorrhagic necrosis of the pancreas is caused by a second enzyme, the fat-splitting enzyme of the pancreatic juice.

Recognition of the fact that necrosis of tissue is the essential feature of the acute hemorrhagic lesion, explains the relation of hemorrhagic to gangrenous pancreatitis. In individuals who die within from one to three or four days after onset of the symptoms, the gland is swollen and hemorrhagic, but when death occurs after a longer period there are changes in the hemorrhagic tissue so that it becomes black and gangrenous in appearance. It has been customary to describe as separate diseases hemorrhagic and gangrenous pancreatitis, whereas in both the underlying change is death of pancreatic parenchyma, and the two conditions represent two stages of the same lesion.

We have recently had the opportunity of studying three cases of acute hemorrhagic pancreatitis, which will be briefly cited because each one illustrates some important fact concerning the etiology or pathology of the disease.

Case I.—M. K., female, aged 34 years, was admitted to the Presbyterian Hospital, in the service of Dr. Eliot, on November 8, 1908. She remembered no past illness. One brother died of acute pulmonary tuberculosis.

Present Illness.—In February, 1908, the patient was suddenly attacked with severe pain in the epigastrium. The pain was sharp and intermittent and was accompanied by vomiting which afforded some relief. The pain lasted about twenty-four hours and completely disappeared but returned after several days. There had been slight jaundice during the whole illness, but it was most marked during the three days before admission when the urine was dark colored. These symptoms continued for about three weeks, and disappeared. About October 1, 1908, she was again attacked with severe, sharp epigastric pain accompanied by vomiting. The pain was continuous and was increased only by deep respiration. There was frequent vomiting, but no jaundice; bowels were regular and feces were normal in appearance. About the middle of October the pain gradually diminished and almost disappeared. October 24, 1908, she had a severe chill followed by sweating.

On entrance to the Hospital the patient was well nourished but very pale; there was no jaundice. In the epigastrium to the right of the midline was a fluctuating, slightly tender mass, 8 cm. in diameter; the overlying skin had been reddened by poultices. The edge of the liver could be felt on either side of the midline and the mass seemed to be connected with this organ.

On November 9, 1908, Dr. Eliot opened the abdomen and evacuated a large abscess apparently connected with the liver. It contained a large quantity of thick, brownish pus, with very little odor. Agar-agar inoculated with this pus remained sterile. After operation the patient did not improve; she vomited frequently and was unable to retain any food. The wound discharged freely and at times masses of grayish, cheesy, necrotic material were found on the dressings. The finger could explore a cavity about 12 cm. in diameter with walls covered by soft necrotic material; to the left no wall could be felt. Microscopical examination of the mass discharged from the wound revealed only necrotic debris.

On November 30, 1908, a second operation was performed. A large cavity was found extending to the posterior parietes and for some distance both to the right and to the left of the midline. There was very little pus but the cavity was lined with necrotic material. The patient did not improve after the second operation and died December 1, 1908.

Temperature after admission to the Hospital ranged from 100 to 104° F., pulse from 100 to 160, and respiration from 20 to 60.

Urine contained a trace of albumin and a few casts; there was no bile nor sugar; there was no leucin nor tyrosin and the pancreatic reaction of Cammidge was negative.

The white blood corpuscles on entrance to the Hospital numbered 14,800 per c.cm. but diminished to 3,000 per c.cm. Progressive diminution of polynuclear leucocytes with increase of transitional forms, large mononuclear leucocytes and lymphocytes is exhibited by the counts on page 567.

Autopsy.—An autopsy was performed 3 hours after death. In the upper right hypochrondrium from the wound of operation there is a deep sinus surrounded by firm adhesions.

In the fat of the omentum over the transverse colon there are numerous, small, white areas of fat necrosis. There are no such foci in the dependent part of the omentum. In the median line the coils of small intestines are adherent

	Nov. 8.	Nov. 16.	Nov. 18.	Nov. 27.	Nov. 28.	Nov. 30.
Total leucocytes per c.cm	14,800	10,700	15,700	4,800	2,750	3,000
Poly. leucocytes	78.5%	77 %		29%	26 %	41.5%
Transitional	6	6		16	27.5	15
Large mononuclears	2	2		21	4	16
Lymphocytes	13	14.5		31	42	25.5
Basophilic	0	0		0	0	0.5
Eosinophilic	0	0		1	1	1.5
Stimulation forms	0.5	0.5		2	0	0

to the base of the mesocolon; after these adhesions are broken an abscess cavity, extending across the abdomen above the transverse mesocolon is exposed. At the base of the mesentery, especially where the loops of the small intestines are adherent to the transverse mesocolon are large plaques of fat necrosis. The gastro-colic omentum forms the anterior boundary of the abscess cavity. The hepatic flexure of the colon is firmly adherent to the liver.

From the opening in the abdominal wall the sinus with necrotic edges passed directly backwards to the duodenum. Over the surface of the duodenum the sinus with walls of black, soft tissue extends a short distance to the right; to the left it communicates with a very large cavity lying in front of the pancreas and representing in part the lesser peritoneal cavity. This cavity lies in great part below the pancreas and stomach which at the splenic end of the gland are tightly bound together. It extends to the left as far as the spleen and lateral abdominal wall. An extension from this cavity passes downward into the retroperitoneal tissues to the left of the root of the mesentery, and in front of the kidney. Erosion in this region has extended into the abdominal wall and has reached to within about 1 cm. of the surface above the crest of the ilium.

Behind the body of the pancreas, extending upward through the retroperitoneal tissue is a second sinus which communicates with an immense cavity above the stomach and immediately below the diaphragm extending from the under surface of the liver to the spleen. The diaphragm to the left of the midline in contact with the abscess cavity is penetrated by an opening 1.5 cm. across. This opening communicates with a localized pleural abscess (7 by 8 cm.) about which the lung is firmly bound to the diaphragm; its wall is covered by shaggy fibrin and it contains foul smelling pus-like fluid. The pulmonary tissue in contact with this cavity is firmer than elsewhere.

In front of the head of the pancreas is the abscess cavity described above; the surface of the gland is here covered by soft, black tissue. This black gangrenous tissue covers the body of the pancreas half way to the splenic extremity whereas the remainder of the anterior surface of the body and tail is adherent to the stomach and shows neither necrosis nor erosion. The abscess cavity which has burrowed underneath the gland about its midpart dissects the greater part of the posterior surface of the splenic half from the underlying retroperitoneal tissue. The pancreas throughout is firm and on section the lobulation is less clearly defined than usual. On the surface and less frequently in the substance of the gland occur opaque, yellow spots of fat necrosis 2 or 3 mm. across. On section through the abscess wall into the head of the pancreas a narrow zone of fibrous tissue is found between the necrotic abscess wall and

the pancreatic parenchyma. The duct of the pancreas is slightly dilated and patulous.

On opening the duodenum the papilla of Vater is conspicuous and measures approximately 3 mm. in diameter; the circumference of the orifice is 12 mm. The common bile duct is somewhat dilated and 1 cm. above the orifice, measures 16 mm. in circumference. The duct of Wirsung joins the common bile duct 7 mm. from its duodenal orifice.

The gall bladder is small and its wall is thick. It contains eleven, small gall stones measuring from 6 to 9 mm. in diameter. One stone is partially enclosed by a saccule at the fundus. The cystic duct is dilated.

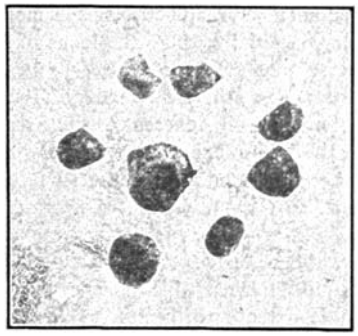

FIG. 1. Showing size of calculi found in gall bladder (Case I). Three stones of approximately same size as the smaller of those shown in the photograph were lost.

The liver weighs 2,275 gm. The surface in contact with the abscess cavity is discolored and covered by necrotic material. The substance is pale and the lobulation is indistinct.

Mucous membrane of the stomach is smooth and pale except for a few submucous hemorrhages. The duodenum is apparently normal. The jejunum is empty.

Culture from the peritoneum contains many varieties of bacteria, including streptococci and B. coli together with other unidentified bacteria. No culture grew from the liver.

Microscopical examination shows that the capsule of the pancreas is much thickened and its outer layers are necrotic. The inner layer consists of vascular granulation tissue in which are hemorrhages. Extending in from the capsule are greatly thickened strands and masses of similar tissue in which there are numerous round cells. In large areas parenchyma is almost wholly replaced and lobules are represented by a few acini. The islands of Langerhans are numerous and large; their capsules are somewhat thickened but there is no increase of connective tissue between the cells. The blood vessels are thickened and hyaline. The walls of the ducts are somewhat thickened; in places the lumen is dilated.

Anatomical Diagnosis.—Hemorrhagic necrosis of the pancreas in process of healing; disseminated fat necrosis; peri-pancreatic abscess with erosion of retroperitoneal tissue; subdiaphragmatic abscess; perforation of the diaphragm; localized diaphragmatic empyema; pneumothorax. Cholelithiasis; chronic cholangitis; fatty degeneration of the liver. Broncho-pneumonia. Fibro-myoma of the uterus.

Several features of the case are especially noteworthy: First, the gall-bladder contains eleven small stones of almost uniform size and the conformation of the common part of the biliary and pancreatic ducts is such that any one of these stones might block the duodenal orifice of the two ducts and divert bile into the pancreatic duct. Such entrance of bile into the pancreas would explain the gangrenous peripancreatitis found at autopsy. A second feature of considerable surgical interest is the tendency of the peripancreatic abscess, at first limited to the lesser peritoneal cavity, to erode the retroperitoneal tissues. The tendency of such abscesses to erode the tissue in front of the left kidney and to point in the lumbar region, is well illustrated by the present case. Incision in this region for counter-drainage has been at times practicable. The abscess cavity in the case just cited had moreover excavated a passage behind the pancreas, and had formed an immense subdiaphragmatic abscess between liver, stomach, diaphragm and spleen. Erosion of the diaphragm had caused complete perforation and had been followed by localized empyema. Such widespread solution of tissue is doubtless referable in part to the tryptic enzyme set free by the injured pancreas.

No growth of bacteria was obtained from the pus found at operation; cultures from the peritoneal cavity at autopsy contained various bacteria among which were Bacillus coli and streptococci. The leucocytes which during the first week after admission to the Hospital numbered approximately 15,000 per cu. mm. rapidly diminished in number and became subnormal just before death.

At autopsy there was no pancreatic necrosis but evidence of destruction of pancratic parenchyma was furnished by bands of dense connective within the gland. When hemorrhagic necrosis produced experimentally in dogs is not fatal parenchyma which undergoes necrosis is absorbed and replaced by newly-formed fibrous

tissue. The same process has doubtless occurred in the case just described. Superficial necrosis of the pancreas with inflammatory changes has been followed by inflammation of the lesser peritoneal cavity with formation of the immense abscess which has been described.

Several years ago one of us[19] showed that a *small* gallstone lodged at the duodenal orifice of the bile papilla might divert bile from the bile duct into the pancreatice duct. A large stone, on the contrary, would fill the common part of the two ducts and obstruct the outflow from both. The gall stone which causes the lesion usually escapes into the intestine and is lost. In the case of hemorrhagic pancreatitis which suggested the occurrence of the mechanism just described, the stone still occluded the common duodenal opening of the two ducts; the pancreatic duct was stained with bile. The earlier literature of the subject contains similar cases and almost identical instances have been recently described by Bunting,[20] and at a recent meeting of the New York Pathological Society, by Crowell. The gall stone which causes the pancreatic lesion usually escapes into the duodenum but in many recorded cases the gall-bladder has contained a large number of uniformly small stones, any one of which might cause the fatal diversion of bile into the pancreatic duct. In the case which we have just reported the gall-bladder contained such small calculi of almost uniform size (Fig. 1).

It has been claimed that gall stones are not more frequently found in association with acute hemorrhagic pancreatitis than in individuals of similar age dying from other diseases. Among eight cases of hemorrhagic necrosis (acute hemorrhagic pancreatitis), which I have had the opportunity of studying, gall stones have been present in five. Among one hundred and five recorded cases collected by Egdahl,[21] cholelithiasis was present in forty-two per cent. This proportion, which may be regarded as an established minimum, is doubtless small, for in many instances data which have been recorded do not exclude the presence of gall-stones. Their presence has not been noted or a single calculus causing the lesion has been

[19] *Loc. cit.*

[20] *Bull. of the Johns Hopkins Hosp.*, 1906, xvii, 265.

[21] *Idem*, 1907, xviii, 130.

lost. According to the statistics collected by Körte,[22] acute hemorrhagic and gangrenous pancreatitis occurs with few exceptions between the ages of twenty and sixty years. According to statistics of Mosher,[23] carefully compiled from German and American sources, the frequency of gall stones between the ages of twenty-one and sixty years is represented by 8.9 per cent. of all autopsies, less than one-fourth of the proportion found with the acute pancreatic lesion.

Whereas it is not improbable that half, or perhaps more than half, of all cases of hemorrhagic necrosis are caused by gall stones, all cases cannot be thus explained. In the following case which occurred in the service of Dr. Eliot at the Presbyterian Hospital, no gall stones were found at autopsy, and the conformation of the pancreatic ducts was such that a gall stone could not have produced the lesion.

CASE II. J. S., was admitted to the Presbyterian Hospital in the service of Dr. Eliot, on October 25, 1908. The patient was male, white, aged 55 years, a coach driver by occupation. One sister died with acute tuberculosis.

The patient has used alcohol in excess; in October, 1906, he had acute alcoholic gastritis and suffered with frequent vomiting and severe diarrhœa; there was hematemesis and considerable melena. The liver was palpable 4 cm. below the costal margin and tender; there was no jaundice. After this illness symptoms of chronic gastritis continued and there was frequent morning vomiting and eructations.

On October 22, 1908, there was sudden, severe epigastric pain followed by vomiting. The pain continued to be severe and extended a little outside the epigastric region. Vomiting was almost continuous and the vomitus had a very dark color but no foul odor. There was constipation. The patient had been dyspneic.

On entrance to the Hospital the patient was almost moribund; the face and hands were cyanotic; there was no jaundice. Temperature was 99.6° F., respiration, 40; pulse, 140. The abdomen was symmetrical and distended but not very tense; it moved little with respirations. There was tenderness and rigidity in the right upper quadrant and in less degree in the left upper quadrant. No mass was palpable. On percussion the right upper quadrant, the upper part of the right flank and the whole of the left flank were dull.

No urine was obtainable for examination.

White blood corpuscles October 25, numbered 9,900 per cu. cm. Differential count: polymorphonuclear leucocytes, 88 per cent.; transitionals, 5 per cent.;

[22] Chirurgische Krankheiten des Pankreas. Deutsche Chirurgie, Stuttgart, 1898.

[23] *Bull. of the Johns Hopkins Hospital*, 1901, xii, 253.

large mononuclear leucocytes, 1 per cent.; lymphocytes, 5 per cent. and eosinophiles 0.5 per cent.

Patient died six hours after entrance to the Hospital.

Autopsy.—An autopsy has been performed fifteen hour after death. The mesentery is studded with small grayish areas of fat necrosis. These areas are most numerous on the right side and many large foci are found in the perirenal fat.

The tail and body of the pancreas are soft, and have a deep, dark red color mottled with lighter, grayish areas. Here and there occur minute whitish spots of fat necrosis. Upon the surface of the body occur a few blackish spots extending into the substance of the gland; they represent the only evidence of hemorrhage. The greater part of the head of the gland shows the same changes and one or two black areas occur; the only part of the gland which has the appearance of normal tissue is situated on the posterior and lower part of the head in contact with the duct of Wirsung.

Liver weighs 3,425 gms. The surface is smooth; the cut surface has a uniform yellow color and the lobulation is distinct. The gall bladder, which measures $11 \times 5\frac{1}{2}$ cm., is distended with rather thick, dark green bile, and contains no stones nor sand. The bile ducts are patent.

Stomach is large; its mucous membrane is in places injected and covered by blackish mucous. The duodenum is normal.

The kidneys show a moderate increase of interestitial tissue; there is general arteriosclerosis. At the apices of both lungs are a few encapsulated, partly caseous nodules. The other viscera are normal in appearance.

Cultures from spleen and liver contain Bacillus coli; aerobic and anaerobic cultures from the pancreas contain only Bacillus coli.

Microscopical Examination of the Pancreas.—A section from the *head* near the duct of Santorini shows complete necrosis and disintegration so that the architecture of the gland is completely lost. In a few small spots parenchyma is well preserved, acini being intact and nuclei well stained. Here interstitial tissue is distended as if by edema, red blood corpuscles are fairly numerous and polynuclear leucocytes occur in small number. At the margin of such areas acini still preserve their form but nuclei have disappeared. In some spots of preserved parenchyma there is slight increase of interstitial tissue. About the duct of Wirsung there is in places necrosis with loss of nuclei but except in a few areas the shape of the acini is recognizable, whereas in the greater part of the section tissue is intact and nuclei are stained. A section from the *body* shows almost complete disintegration similar to that about the duct of Santorini. An area of intact tissue shows considerable increase of connective tissue in great part about the lobules; this tissue contains numerous lymphoid cells and red blood corpuscles and a few polynuclear leucocytes. Tissue in the *tail* of the gland is in part necrotic and disintegrated, in part living. The preserved tissue is in places infiltrated with red blood corpuscles. Well preserved islands of Langerhans occur in fair abundance. Small veins contain thrombi.

Anatomical Diagnosis.—Hemorrhagic necrosis of the pancreas; chronic interstitial pancreatitis; fat necrosis; chronic pulmonary tuberculosis; chronic interstitial nephritis; fatty degeneration of the liver; arteriosclerosis.

In Case II death occurred only three days after onset of the symptoms which were such as usually accompany acute hemorrhagic necrosis of the pancreas. Pancreatic parenchyma has undergone almost complete necroses; there are trivial inflammatory changes at the margin of the necrotic tissue and in the neighboring abdominal fat are widely scattered foci of necrosis; the lesion has the characters found with so-called acute hemorrhagic pancreatitis yet hemorrhage is almost wholly wanting. The altered tissue is not visibly infiltrated with blood and minute black spots sparsely scattered upon the surface of the gland represent the only evidence of ecchymosis. Microscopic examination shows that there has been some escape of blood into the interstitial tissue of that parenchyma which is still intact.

The ducts of the pancreas exhibit an anomalous arrangement. The duct of Wirsung, which joins the common bile duct, is of small size and drains only a small part of the head of the gland; this area appears to be the least changed part of the organ. The duct of Santorini, which constantly enters the duodenum nearer the stomach than the duct of Wirsung, and is usually a small accessory duct (see Fig. 2), is in this instance the chief outlet of the gland, and, far larger than the duct of Wirsung, traverses the entire length of the pancreas (see Fig. 3). The orifice of this duct readily admits a probe about two millimeters in diameter. The gall-bladder and bile passages contain no calculi.

Since the duct of Wirsung is relatively small, whereas the main duct of the gland enters the duodenum about 1.5 cm. from the common bile duct, bile could enter only a small part of the pancreas. On the other hand, it is not improbable that an anomalous duct opening by a relatively wide orifice, might have been the portal of entry for material from the duodenum. The power of such material to cause acute hemorrhagic pancreatitis has been repeatedly shown by experiments. Hlava, who showed that acid gastric contents injected into the pancreatic duct causes the lesion, has suggested that antiperistaltic movements of the intestine might drive gastric or duodenal contents into the pancreatic ducts; there is no evidence that the lesion is produced in this way. The discovery of enterokinase in the intestinal juice has suggested that self-diges-

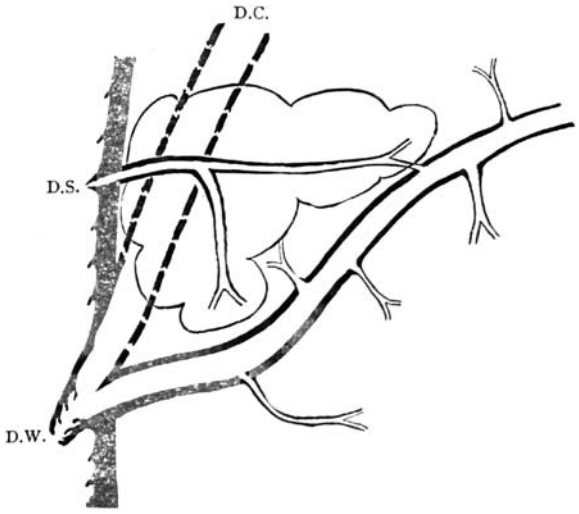

FIG. 2. Diagram showing the usual relative size of the duct of Wirsung (D.W.) and duct of Santorini (D.S.); the duct of Wirsung joins the common bile duct (D.C.).

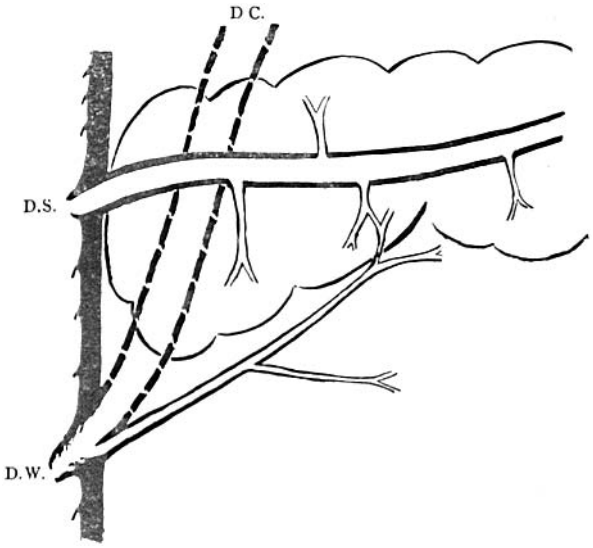

FIG. 3. Diagram showing the relative size of the two pancreatic ducts in Case II. The part of the gland drained by the duct of Santorini is indicated in both diagrams by curved lines.

tion of the pancreas might occur during life should enterokinase find its way into the pancreas. The part played by enterokinase is somewhat doubtful (Pólya, Williams and Busch),[24] but several experimenters (Pólya, Hess) have shown that small quantities of duodenal contents injected into the pancreatic duct will produce acute pancreatic necrosis with fat necrosis.

It is well known that increased pressure within the duodenum does not force duodenal contents into the bile duct or into the pancreatic duct after death. The delicate valves found within the diverticulum of Vater are believed to prevent regurgitation. In approximately one of ten individuals,[25] what is usually the accessory duct of the pancreas, namely, the duct of Santorini, is the chief outlet of the gland and is larger than the duct of Wirsung which joins the common bile duct (Fig. 3). The orifice of such an anomalous duct is perhaps unable to prevent regurgitation of intestinal contents when pressure within the duodenum is increased by vomiting. In the case which I have just described this anomaly has existed and perhaps explains the occurrence of the pancreatic lesion.

Cases recorded in the literature of the subject give some support to this view. Johnstone[26] has described two cases of acute pancreatitis in which the pancreatic duct has opened into the duodenum 1 or 2 cm. from the common bile duct, and although he has described these cases with the purpose of showing that gall stones have not been an etiological factor in the production of the lesion, he does not suggest that the anomalous condition may explain its occurrence. The description of this author makes it probable that the arrangement of the ducts in these two cases resembles that which I have just described. In an additional case described by the same author the distribution of the ducts is not described, whereas in a fourth case the nature of the lesion described is doubtful.

Further evidence that the duct of Santorini may be a portal of entry for irritant material from the duodenum is furnished by a case of Bassett.[27] The two ducts of the gland bore the usual relation to

[24] *Trans. of the Assn. of Am. Phys.*, 1907, xxii, 304.
[25] Opie, Disease of the Pancreas, Philadelphia, 1903, p. 30.
[26] *Colorado Med.*, 1907, iv, 93.
[27] *Trans. of the Chicago Path. Soc.*, 1907, vii, 83.

one another (Fig. 2); the duct of Santorini was much smaller than the duct of Wirsung and drained only a small part of the gland. This duct terminated at the margin of an anomalous duodenal diverticulum of which the mucosa was inflamed. Limited to the immediate neighborhood of this small duct was hemorrhagic pancreatitis with fat necrosis. The patency of the orifice of the duct of Santorini was not demonstrated. In the case which I have described almost the entire gland, of which the chief outlet was the duct of Santorini, was the seat of hemorrhagic inflammation, and the part about the small duct of Wirsung was apparently the least changed part of the organ, whereas in the case of Bassett, with a small duct of Santorini terminating in an anomalous diverticulum, the lesion was limited to the small area drained by this duct. (The domain of the duct of Santorini in the usual and in the anomalous condition is indicated in Figs. 2 and 3.) Although these cases do not afford conclusive proof that duodenal contents causes the lesion, they suggest this possibility with such force that a careful study of the topography of the ducts in cases of hemorrhagic necrosis of the pancreas is desirable.

The etiology in all instances of acute hemorrhagic pancreatitis is not the same. This fact is further emphasized by the occurrence of a small group of cases in which the lesion has so quickly followed abdominal injury in the epigastric region that its relation to traumatism cannot be doubted. A typical case is described by Selberg.[28] A man was kicked over the stomach by a horse and was unconscious for a time. There was pain and gradual distention in the epigastric region together with vomiting. Death occurred after twenty days. The omentum was studded with fat necrosis; the pancreas was infiltrated with blood and was gangrenous in appearance. In the following case localized hemorrhagic necrosis of the pancreas with localized fat necrosis followed a stab wound of the abdomen.

CASE III.—J. T., male, aged 20 years, was stabbed on the afternoon of November 4, 1908, in the upper left quadrant of the abdomen with a long stiletto. After about ten minutes he vomited, but there was no blood in the vomitus. Vomiting was followed by nausea. At the site of the wound there was considerable pain, which was increased by breathing.

[28] *Berl. klin. Wchnschr.*, 1901, xxxviii, 923.

On entrance to the Hospital a short time after the injury the temperature was 100.6°; pulse, 96; respirations, 16. The heart and lungs were found normal. Just above the costal margin in the left mammillary line there was a horizontal stab wound one inch long and parallel to the ribs; through the wound projected a mass of omentum, about the size of an egg. There was slight swelling about the wound but very little tenderness. There was no evidence of fluid in the abdomen.

Exploratory operation was performed November 4, 1908. The stab wound in the left costal space perforated the diaphragm, but the pleura was not injured. Upon the antero-lateral surface of the stomach was a perforation 1.5 cm. long through which a small amount of fluid had escaped. The posterior wall was apparently normal. The peritoneal cavity contained a large amount of fluid and clotted blood. The intestines and other viscera were apparently uninjured. The perforation in the anterior wall of the stomach was closed by sutures.

During the succeeding days the temperature varied between 101° and 106°, and the pulse was very rapid. There was frequent nausea and vomiting. There was distention of the abdomen, althought the bowels moved freely and considerable flatus was expelled. Discharge from the wound was profuse. The patient gradually became weaker and died November 9.

Streptococci in pure culture were found in the peritoneal exudate. A blood culture remained sterile.

White blood corpuscles numbered from 3,000 to 7,000 per c.mm.

The urine contained a faint trace of albumin and a few casts.

Autopsy was performed by Dr. Schutz, coroner's physician. Throughout the peritoneal cavity is fibrino-purulent exudate. The wound of the antero-lateral wall of the stomach has remained closed and is in process of healing. There is no perforation of the posterior wall of the stomach, but opposite to the wound in the anterior wall there is upon the mucosa of the posterior wall a circular spot of edema and injection 2.5 cm. in diameter; a minute central area of necrosis about the size of a pin's head, evidently represents the spot in which the point of the knife had struck. Upon the surface of the pancreas immediately behind this wound is a localized hemorrhagic area about 3.5 cm. in diameter and in the fat of this area are conspicuous foci of fat necrosis. Otherwise the pancreas appeared normal.

Microscopic examination of the hemorrhagic area in the pancreas shows hyaline necrosis of the pancreatic parenchyma similar to that frequently observed with so-called acute hemorrhagic pancreatitis; the interstitial tissue is infiltrated with blood and in places contains polynuclear leucocytes. The veins within the hemorrhagic zone are widely dilated and contain thrombi.

It is noteworthy that simple injury to the pancreas of animals fails to produce necrosis, whereas injury associated with occlusion of blood vessels is followed by changes which resemble those of hemorrhagic necrosis (see p. 563). Trivial injury to the pancreas is usually followed by rapid healing but in Case III injury was associated with pancreatic necrosis, hemorrhage, slight inflammation

and focal fat necrosis. It is not improbable that the simultaneous occurrence of localized venous thrombosis and pancreatic injury, both due to a stab wound, explains the occurrence of hemorrhagic necrosis of pancreatic parenchyma.

The lesion usually designated acute hemorrhagic pancreatitis is primarily necrosis of the pancreatic parenchyma and may be caused by various, usually chemical, occasionally mechanical, injuries to the gland. The name hemorrhagic necrosis is preferable to acute hemorrhagic pancreatitis because the lesion is essentially widespread necrosis of the pancreatic parenchyma and the inflammatory changes which occur are secondary to necrosis or subsequent to bacterial infection.

The pancreas is not more susceptible to spontaneous hemorrhage than other organs; so-called pancreatic apoplexy is the result of acute pancreatic necrosis. In some instances pancreatic necrosis (Case II) may cause little if any hemorrhage. So-called gangrenous pancreatitis is a late stage of hemorrhagic necrosis.

Hemorrhagic necrosis of the pancreas is not primarily the result of bacterial infection, but in some instances subsequent infection of gangrenous tissue may cause suppuration.

The most frequent cause of hemorrhagic necrosis of the pancreas in man is penetration of irritant material into the ducts of the pancreas. Bile diverted by a gall stone lodged at the duodenal orifice of the common bile duct has produced the lesion in a large proportion of cases; duodenal contents entering the duct may have the same result. In a small proportion of cases pancreatic necrosis follows injury to the gland and is perhaps in part referable to simultaneous thrombosis of blood vessels.

Certain individuals are rendered susceptible to hemorrhagic necrosis of the pancreas by anatomical peculiarities or anomalies of their pancreatic ducts. In some individuals the passage of a gall stone may divert bile into the pancreas; in others perhaps the structure of the ducts may be such that duodenal contents can find its way into the pancreatic ducts, and thus cause the disease.