The Adult Pancreas in Trauma and Disease

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ABSTRACT

The spectrum of traumatic and natural disease that can affect the adult pancreas is multiple and varied. Some entities are more commonly encountered in routine forensic pathology practice and the forensic pathologist needs to be very familiar with their pathological features and development from a pathophysiological perspective. However, many of the conditions are extremely rare and may never be encountered in the professional lifetimes of an individual pathologist. Still, forensic pathologists need to be aware of them in case they are one day faced with these entities as possible diagnoses to be established at postmortem examination. This can be the result of clinical concerns raised in life, potential natural disease explanations for unexpected biochemical results, and sudden, unexpected or otherwise unexplained deaths where criminal concern about the exogenous administration of a substance must be considered. *Acad Forensic Pathol.* 2018 8(2): 192-218

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INTRODUCTION

Anatomy of the Pancreas

The pancreas is an elongated, soft, tan-grey digestive gland of 12-15 cm length, which is located more or less transversely in the retroperitoneal space across the posterior abdominal wall in the upper part of the abdomen, within the epigastric and left hypochondrial regions. It has both exocrine and endocrine functions. Its exocrine function is manifested in its production of pancreatic juice which enters the duodenum via the pancreatic duct to aid in digestion, and its endocrine function is reflected in its production of glucagon and insulin which enter the bloodstream (1).

The pancreas crosses the midline plane of the body and consists of a head, neck, body, and tail. Its passage across the midline unevenly divides it into left and right segments with its right segment lying across the bodies of the L1 to L3 vertebrae. Its head is located within the C-curve of the duodenum and is embraced by it. The head of the pancreas rests posteriorly on the inferior vena cava, the right renal vessels, and the left renal vein, and exhibits a superior prolongation called the uncinate process.

The neck of the pancreas is about 2 cm long and is continuous with the head and merges imperceptibly into the body. The body of the pancreas extends slightly superiorly as it extends to the left side of the body across the aorta and superior lumbar vertebra. The body of the pancreas is intimately related to the stomach. The tail of the pancreas is its narrow, leftward-end that crosses the upper pole of the left kidney and ends in the hilum of the spleen. The splenic artery runs along the superior border of the pancreas towards the spleen (**Figures 1 and 2**).

The exocrine function of the pancreas is facilitated by secretions into the main pancreatic duct. The pancreatic duct begins in the tail of the pancreas and runs through its parenchyma from left to right and is joined by tributaries along its course. Within the pancreatic head, the main pancreatic duct turns inferiorly and comes into close relationship with the common bile

duct. The pancreatic and common bile ducts pierce the posteromedial wall of the second part of the duodenum in an oblique manner near its middle, usually uniting to form a short dilated hepatopancreatic ampulla (ampulla of Vater), which usually opens via a common channel into the duodenum at the summit of the major duodenal papilla.

DISCUSSION

Traumatic Injury of the Pancreas

Pancreatic injury occurs in less than 5% of major abdominal injuries (2). Pancreatic injury may occur from blunt force trauma (e.g., assaults, motor vehicular accidents) or penetrating injury (e.g., gunshot wounds or stabbings) (3).

The posterior position of the pancreas within the abdomen and its considerable distance from the anterior abdominal wall preclude it from frequent blunt force injury. As such, the duodenum and pancreas are relatively well protected because of their deep location in the abdomen. Consequently, injury of the pancreas and duodenum is often associated with severe injuries of other structures (4).

However, since the third part of the duodenum, neck, and body of the pancreas are located immediately in front of the rigid bony vertebral column, they are very susceptible to crushing injuries with the application of blunt force along the anteroposterior plane, with resultant compression these structures against the rigid bony vertebrae such that laceration and/or contusion of these structures occur (5).

The second part of the duodenum is also vulnerable to blows to the central abdomen, since deep to that area the duodenum also crosses the midline and is liable to be sandwiched between the compressed anterior abdominal wall and the promontory of the lumbar spine with resultant perforation or laceration.

The application of a severe, localized blunt force to the epigastrium can result in pancreatic injury. The pancreatic injury can be sustained at the point where

the pancreas overlies the lumbar vertebra. On receipt of a direct blow to the abdomen, the pancreas is prone to percuss the rachidian relief. Since the pancreas is closely connected to adjoining organs, it is relatively fixed and does not benefit from any shock absorption effect and can be severely injured or even ruptured when forced against the vertebral column (6). Contusions, lacerations, and transections can occur. Spill-

age of pancreatic secretions into the abdominal cavity secondary to lacerations of the pancreas will result in chemical peritonitis as a concomitant sequela of associated injury to the pancreatic ducts.

Clinically, traumatic pancreatic lesions are classified according to the Hervé and Arrighi classification as follows:

Figure 1: Diagrammatic representation of the pancreas and its relation to neighboring structures (anterior view). Created under contract by professional medical illustrator Diana Kryski.

Grade I: Contusion/hematoma with integrity of the duct system.

Grade II: Distal rupture of the gland.

Grade III: Proximal rupture of the gland with duct lesions or cross cutting without blow on the duodenum.

Grade IV: Laceration of the cephalic part of the pancreas.

The type of lesion sustained may primarily depend on the impact angle. Direct blows to the abdomen will result in median grade III injuries, whereas lateral impact will cause injuries of either the head or body of the pancreas from either right- or left-sided trauma, respectively (2).

The diagnosis of traumatic pancreatic lesions is often delayed. However, rapid death can occur and when it does, it is generally ascribed to the associated lesions through hemorrhagic shock or peritonitis (7), which would account for a death rate of more than 20% (8).

Figure 2: Diagrammatic representation of the pancreas and its relation to neighboring structures (posterior view). Created under contract by professional medical illustrator Diana Kryski.

Several authors have stated that isolated trauma of the pancreas cannot be responsible for a rapid death (8–10) but can result in numerous complications in 19–25% of cases (11, 12) from fistula formation, acute pancreatitis, pancreatic pseudocyst, and abscess formation with an estimated rate of delayed death of 9% (10, 13). The predictable complications are explained by a combination of rupture of the proximal acini with associated partial digestion of the gland by release of its enzymes. It has been reported that this phenomenon may be delayed for 12 days and up to six months, and is classically not involved in premature deaths (8, 10, 11).

Rougé-Maillart et al. reported a case of fatal blunt pancreatic trauma secondary to assault and battery in which complete destruction of the pancreatic head with massive necrosis of the gland resulted in death six to eight hours after the victim had been hit (6). In their opinion, their case confirmed the reports of others that pancreatic lesions caused by direct trauma to the abdomen, especially from blows in the context of violence, may be rapidly fatal even if isolated because of the high severity of the necrosis they may induce (6, 14, 15). As such, an isolated pancreatic injury can result in rapid death because of the particular type of pancreatic rupture frequently involved (6).

Peripancreatic and intrapancreatic pseudocysts can be

a complication of pancreatic injury (16, 17). A pancreatic pseudocyst is filled with blood and pancreatic secretions and accumulates around the pancreas in the form of a peripancreatic hematoma that resolves to give a cystic lesion filled with clear fluid, the wall of which is devoid of an epithelial lining. This is in contrast to a neoplastic or congenital cyst, which will have an epithelial lining. The wall of the pseudocyst will contain numerous hemosiderin-laden macrophages within fibrous connective tissue. Intrapane-atic pseudocysts develop from intrapancreatic hematomas as a result of intrapancreatic hemorrhage, but again their walls are devoid of an epithelial lining and will contain hemosiderin (16).

Because of its close anatomical relationship with the duodenum, traumatic injury of the pancreas may co-exist with traumatic injury of the duodenum and this is reflected in the American Association for the Surgery of Trauma (AAST) classifications of duodenal and pancreatic injury where combined pancreatic and duodenal disruption has been classified as a grade 4 lesion under both categories (18, 19).

Direct blows to the abdomen in the form of stamping, kicking, forceful blows with a clenched fist, impact from bicycle handle bars, and compression from the lap belt portion of seatbelts are all capable of causing injury (**Image 1**). Severe or fatal intraabdominal in-

Image 1: A) Patterned footwear mark on the lateral aspect of the abdomen of a decomposed male decedent who died from blunt force head injury with a large acute subdural hematoma. **B)** A large contusion of the mesentery was evident on internal examination. (Images courtesy of Dr. Matt Lyall, Home Office Pathologist, United Kingdom).

jury can exist without any discernible external signs of injury, especially if the blunt impact blow has been inflicted through clothing or has been applied over a large area (20). However, injury may be manifested as either cutaneous and/or subcutaneous bruising.

Pancreatic injuries are much less common in children but may occur in vehicular collisions due to the incorrect placement of seatbelts. Although death in the setting of pancreatic trauma is more often due to injuries elsewhere (for example head and chest), pancreaticoduodenal injuries can be lethal in themselves (21). In pediatric pathology, injuries of the duodenum account for less than 5% of intra-abdominal injuries, due to its relatively protective position in the retroperitoneal and duodenal hematomas. Lacerations and perforations should raise concern about the possibility of inflicted injury if no plausible explanation can be provided (22, 23). Pancreatic injury in children is dealt with elsewhere in this edition (24).

Mallick and Thoufeeq reported a case of a 40-year-old woman with a thin body habitus who presented with a two-day history of constant epigastric pain that radiated to her back (25). There was no history of alcohol ingestion or abdominal trauma. Abdominal tenderness and guarding of the epigastrium were evident on physical examination. Blood investigations revealed a normal white cell count but an elevated serum amylase concentration of 404 IU/L (normal range: 0-70 IU/L). A provisional diagnosis of acute pancreatitis was made. Ultrasonography of the abdomen identified a collection of fluid between the spleen and the diaphragm; no gallstones were evident. Computed tomography scans of the abdomen identified a vertical tear in the tail of the pancreas with an intact main pancreatic duct. The other abdominal viscera were normal. She was hemodynamically stable and was managed conservatively with an excellent outcome without complications. Although she had initially denied any history of abdominal trauma, further questioning unearthed an incident two days prior to her onset of symptoms in which she had accidentally collided into the edge of a door frame whilst carrying a medical textbook in front of her abdomen. She had considered the incident to be too trivial to report at

the time of initial presentation. As this was the only plausible traumatic event that she could relate to the onset of her symptoms, the medical team ascribed this incident as the underlying cause of her presentation, but in my opinion the validity of this association is highly dubious.

Mechanism of Pancreatic and Duodenal Injury

The application of blunt force to the body involves inward displacement of the tissues as the primary mechanism of energy transfer. Experimental animal models have shown that blunt impact to the torso produces very little rebound velocity, thereby inferring that bodies are viscous and this can be extrapolated to the human body, which is considered viscoelastic. This viscoelasticity means that displacement upon impact is rate-dependent with the rate and magnitude of the distortion of the body wall determining the nature and severity of the internal injury. Little or no injury may develop on a slow velocity of compression, even with severe inward displacement, while rapid compression may produce severe internal injury with compression of only a small area, although it is recognized that prolonged compression may also be associated with severe injury (26).

Mechanical compromise of the affected tissues in the propagation of different types of waves (e.g., stress, shock, and shear waves) into the body are the factors that determine the likelihood of injury being sustained, as well as crush injury (27). More damage will occur when a localized force is applied in contrast with diffuse application of a force of the same magnitude. As a general principle, solid abdominal organs are more susceptible to blunt force injury than hollow organs. The application of large, relatively static loads to the body give rise to crush injuries as can occur with compression of the anterior abdominal wall towards the retroperitoneum (27).

Shock waves are high-pressure, high velocity waves that travel faster than the speed of sound and can be encountered in explosions (28). Stress (compression) waves are the most common mechanism of injury in high-speed collisions in which impact speeds are

greater than 106 kph, or 66 mph. Shear waves are transverse waves of longer duration but low velocity in which injuries arise from the collision of viscera against non-elastic structures, the asynchronous motion of adjacent connected structures, or stretching (strain) at the site of attachment. This mechanism of injury may be associated with contusions or lacerations of the mesentery, splenic pedicle, the liver at the falciform ligament, and the aorta at the ligamentum arteriosum. Shear wave injury is the most common type of impact injury seen at lower velocity (less than 53 kph or 33 mph) motor vehicular collisions (27). Crush injuries arise from the application of large, relatively static loads to the body (27).

Blunt force injury of the pancreas may be frighteningly symptom-free but the more common scenario will consist of the clinical manifestation of severe peritoneal irritation (3). As such, blunt force injuries of the pancreas may not be picked up immediately and can result in higher rates of morbidity and mortality (3). The biochemical determination of the serum amylase concentration is notorious for being manifestly unreliable in making the diagnosis and can even be normal, even in the presence of disruption of the pancreatic ductal system (3). Injury of the distal aspect of the pancreas carries a much better prognosis than proximal injury, especially when there is associated breach of the major pancreatic ductal system (28).

The complications of pancreatic injury are bleeding, abscess formation, recurrent pancreatitis, fistula formation, and pancreatic pseudocysts (29). Death is usually from sepsis, late hemorrhage, and pancreatic necrosis secondary to acute pancreatitis. As previously stated, pancreatic pseudocysts may complicate blunt abdominal trauma (16, 17).

Complications of Pancreatic Injury – Illustrative Case

The author has seen a case of a 20-year-old young woman who died in an overseas jurisdiction where a forensic postmortem examination had been performed. Her body was repatriated to her home country where a second postmortem examination was conducted at the

request of the local coroner. The circumstances of the death were such that the decedent had been admitted to a hospital with a four-day history of constipation and dehydration. It was alleged that she had fallen onto a drinking glass or bottle eight days prior to her presentation to hospital, but had only begun to feel unwell four days prior to presentation. An emergency laparotomy was performed but she died the following day in the intensive care unit. The forensic postmortem examination listed her cause of death as biliary peritonitis due to contusion of the head of pancreas due to abdominal injuries and the manner of death was classified as homicide. The decedent's boyfriend was arrested, charged, and prosecuted in relation to her death and was subsequently found guilty at trial. The account provided by her boyfriend was that the decedent had been out drinking with friends and had fallen onto a glass to cause the injuries. Later, that account was changed to indicate that she had fallen onto her elbow whilst she had been adjusting her clothes and her own fist had inadvertently rammed into her abdomen as a result.

At the first postmortem examination, two wide bruises with an “arch-like shape” and dark colored edges were identified on the anterior abdominal wall and were attributed to having been caused by a dull object. The abdominal cavity exhibited diffuse white-yellow, chalky fat necrosis of the peripancreatic fat, the omentum, and mesentery with a mesenteric bruise (**Images 2 and 3**). A recent surgically repaired traumatic lacer-

Image 2: Inflammation of the peritoneum with fat necrosis (saponification) (arrows) of the mesentery.

Image 3: Mesenteric bruise (yellow arrow) and fat necrosis (saponification) (white arrows) of the mesentery.

Image 4: Sutured laceration of the liver.

ation of the liver close to the round ligament (**Image 4**) and lacerations of the head of the pancreas with rupture of the major pancreatic duct close to the ampulla of Vater were identified, with extensive hemorrhagic infiltration and fat necrosis on sectioning. There was a wide communication between the lesser omental pouch and the retroperitoneum that contained a collection of 400 mL of bile stained fluid within the retroperitoneum.

Retrospective review of the translated medical/surgical notes indicated that the decedent had undergone an emergency laparotomy in which rupture of the cystic duct and liver had been diagnosed intraoperatively and cholecystostomy, suturing of the liver, and abdominal washout had been performed. Intraoperative cholangiography had raised the possibility of rupture of the cystic duct and that investigation was followed by intraoperative gastroscopy which had supported that impression.

Images of the multi-slice CT scans of the abdomen and pelvis, which had been performed on admission to hospital (without and with contrast enhancement), were obtained, reviewed, and reported on by a radiologist in the jurisdiction of repatriation. The radiological findings and opinions were that there was a clear complex laceration of the pancreatic head and neck with significant retroperitoneal fluid almost obliterating the perinephric fat. The body and tail of the pancreas appeared normal. There was extensive free fluid in the peritoneal cavity which had extended retroperitoneally downwards on the right side to the right paracolic gutter and right pelvic side wall. The small bowel loops appeared rather thick-walled from either inflammation or ischemia. No free intraperitoneal gas was present. The liver, spleen, kidneys, and bones were uninjured. The CT findings were considered entirely in keeping with the findings demonstrated at initial postmortem examination, which consisted of of a pancreatic laceration and extension of free fluid throughout the abdomen and was quite compatible with an extensive bile leak. The extensive retroperitoneal collections around the right kidney and in the right flank, which had spread downwards extra-peritoneally, to the right pelvic side wall, were interpreted

ed as collections of bile attributable to a putative late presentation some seven days after the injury.

The second postmortem examination was performed on the repatriated, previously autopsied body without the benefit of the medical/surgical notes, the detailed postmortem reports, and postmortem photographs were subsequently obtained.

External examination of the body at the second postmortem examination identified a large area of healing abrasions of the back of the right elbow (**Image 5**) with healing, smaller, short linear abrasions on the back of the right forearm. No cutaneous or subcutaneous bruising of the center of the upper abdomen/epigastrium was evident; only a 2 x 1.5 cm recent subcutaneous bruise of the upper right quadrant of the abdomen was identified. Internal examination revealed features of biliary peritonitis associated with an apparent large mesenteric contusion. Some pancreatic tissue with a previously opened segment of common bile duct was identified but that pancreatic tissue did not exhibit any signs of inflammation or injury; however, the head of the pancreas was absent.

All the major organs and tissues appeared to have been repatriated with the body, but the esophagus and duodenum were not identified and the kidney and pancreas were incomplete. The duodenum and head of pancreas were believed to have been either excised at laparotomy or retained at postmortem examination for formalin fixation and histological examination. No cutaneous or subcutaneous bruise of the central abdominal area was identified at second examination to account for the internal abdominal injuries.

Image 5: Abrasions on the back of the right elbow.

Microscopic examination of the tissues taken for histological examination at the second examination confirmed acute biliary peritonitis with lipolytic fat necrosis of the abdominal cavity. No chronic or acute pancreatitis was evident in the examined sections of normal-looking pancreatic tissue that was present in the body. Histological examination of the areas of tissue hemorrhage in the abdominal wall and mesenteric tissue confirmed extravasation of red blood cells but no associated inflammatory reaction was evident and iron stains were negative. If any of those areas had represented true bruising, they would have had to have been sustained within two to three days, and given that the decedent had undergone abdominal surgery and postmortem examination in the overseas jurisdiction, these areas were considered unrelated to any abdominal impact five or more days prior to death. The histological sections from the original postmortem examination were not provided for review because of the criminal trial in that jurisdiction, despite official requests for the same to be obtained.

The conclusions of the second postmortem examination were in concert with those of the initial examination in that the young woman had died from the systemic complications of biliary peritonitis that had developed from traumatic blunt force impact of the abdomen with injuries of the head of the pancreas in the form of contusions and lacerations, which had been sustained by the application of a severe degree of blunt force to the anterior abdomen. The surgically diagnosed rupture of the cystic duct had permitted leakage of bile into the peritoneal cavity with the resultant bile-induced inflammatory response of the peritoneum (biliary peritonitis).

The mechanism of injury was the application of a severe degree of blunt force to the anterior abdominal wall that resulted in compression of the abdominal wall and underlying intraabdominal viscera against the rigid vertebral column in a “hammer and anvil manner” to effect crush injury on the liver and head of pancreas. Severe forceful blow(s) to the abdomen in the form of stamp(s) with a shod foot, kick(s), or a clenched fist were the most likely cause of the spectrum of injury but other mechanisms of forceful compressive blows

to the abdomen were also possible. It was not conceivable that a fall from a standing height onto either a drinking glass, a bottle, or the decedent's clenched fist could have generated enough force to produce the spectrum of severe injuries identified intraoperatively or adequately explain their development.

The alleged fall onto a bottle or her own fist four days prior to her reported symptoms of feeling unwell appeared to be a rather long delay in presentation and was considered an atypical presentation of the spectrum of intraabdominal injuries sustained. If the fall onto a bottle were a feasible cause of the intraabdominal injuries, the expected clinical presentation of the peritonitis should have developed over the course of a few hours and not after four days, but it was recommended that the clinical opinion of a consultant general surgeon should be sought in that regard. From the available information gathered at the second postmortem examination, the cause of death was given as biliary peritonitis due to contusion and laceration of the head of the pancreas due to blunt force trauma of the abdomen.

A third postmortem examination was performed by another forensic pathologist in the jurisdiction of repatriation acting on the instructions of a lawyer who was seeking the interest of the accused in the overseas jurisdiction. That forensic pathologist concluded that the cause of death was straightforward from a medical point of view and agreed that the decedent had died from complications of traumatic injury of the head of the pancreas secondary to a substantial impact to the front of the abdomen. He opined that the causative impact could have been a punch or a fall onto an object or other projecting surface. It was stated that there was no convincing medical evidence of abdominal wall bruising attributable to the original impact and stated that the naked eye and microscopic autopsy findings indicated that the causative impact had occurred days prior to death, with five to eleven days being within the possible timescale, but with the caveat that the clinical history may further assist in determining a likely timescale. It must be noted that this expert opinion had also been provided without the benefit of reviewing the histology sections from the original postmortem examination.

The expert opinion of a professor of upper gastrointestinal tract, pancreatic, and biliary surgery was sought. That opinion stated that the alleged account of how the injury was sustained was plausible. In providing that opinion, the accounts of eight friends and the decedent's boyfriend were considered. It was stated in that expert report that the decedent had allegedly fallen twice on the same day. The description of the first fall was the decedent had tripped and fallen forwards whilst she had been out drinking with friends. She had apparently fallen full length without attempting to break the fall. It appears that she may have had a drinking glass in her right hand at the time of the fall and had been attempting to adjust her clothes with her hand, which was inside her belt. After the fall, she complained that she had hurt her right side but had carried on drinking before going home. The account of the second fall was more speculative in that she may have fallen on a set of spiral stairs in her apartment on arrival home. The professor of general surgery stated in his report that:

...the likely mechanism involved was that the decedent's arm had been driven upwards into her right upper quadrant to cause the pancreatic injury by the force of the impact. The effect of the alcohol that she had drunk had contributed to her failure to react to save herself in the fall and had probably dulled the response of the abdominal muscles, thereby reducing the protection given to the internal organs.

Three years later, the professor of surgery produced an addendum to his initial report where it was stated he had now seen evidence that the decedent had not fallen onto the glass she had been allegedly holding in her right hand at the time of the fall. However, he reiterated his conclusion that a fall onto her elbow whilst inebriated could have pushed her hand into the right upper quadrant of her abdomen with sufficient force to injure the pancreas and stated this mechanism was most consistent with the clinical picture and development of the illness over the following eight to ten days. In his opinion, in the absence of any other documented injuries, this allegedly witnessed fall remained the only possible cause of the pancreatic injury and explanation for her death.

The overseas court rejected the defense of a fall being responsible for the injury and found the boyfriend guilty of murder. A coronial inquest subsequently occurred in the jurisdiction in which the body had been repatriated at the request of the defendant and the outcome of the inquest was in line with the determination of the overseas court at the criminal trial.

Spectrum of Natural Disease and Nontraumatic Conditions in the Adult Pancreas

Autolysis and the Pancreas

Postmortem autolysis is defined as the spontaneous destruction of cells or tissues by lysosomal enzymes after death (30). The pancreas is well known to be one of the organs most susceptible to postmortem autolysis due to its abundant content of enzymes. Its autolysis can be rapid and interfere with histological examination of pancreatic lesions. It is rare for the pancreas to be extremely well preserved at postmortem (**Image 6**). While not a disease, autolysis must be distinguished from disease.

Morphologically, autolysis is determined by degeneration of the cells without an associated inflammatory reaction, especially a lack of neutrophils (31). Cellular necrosis is adjudged by the combination of either nuclear pyknosis, karyorrhexis, or karyolysis, and increased eosinophilia of the cytoplasm (31). In general

terms, greater degrees of autolysis are seen in lengthened postmortem intervals (32).

The changes in cell nuclei after death generally indicate the breakdown of nucleoproteins by enzymes, although no trypsin activity in the pancreatic tissue has been reported to occur during in vitro postmortem autolysis (33). One of the most important enzymes is cathepsin, an intracellular proteinase found in most animal tissues and is most abundant in the liver, kidney, and spleen (34). Cathepsin is inactivated by formalin and formalin fixation of tissues prevents further autolysis by inactivation of intracellular enzyme activity (34).

Postmortem autolysis is influenced by both the body and environmental temperatures and is delayed by low temperatures (30). It has also been suggested that the degree of autolysis is influenced by several other factors including the cause of death (35).

Shimizu et al. assessed the histological features of the pancreas for autolysis in 92 autopsy cases by sections taken from the head, body, and tail (32). They classified the degree of autolysis as zero degree (no autolysis), first degree (up to $\frac{1}{3}$ of the section), second degree (between first and third degree), and third degree (greater than $\frac{2}{3}$ of the section), with the final degree of autolysis expressed as the mean value for three sampled sites (head, body and tail). The degree of autol-

Image 6: Sections of well preserved pancreas **A**) and **B**) (H&E, x50).

ysis was then compared against the clinical data and other information for every case. Their findings supported the generalization that more extensive autolysis is seen with lengthening of the postmortem interval but some outliers were also observed. The pancreas was either unexpectedly well preserved or poorly preserved in a few cases, irrespective of the postmortem intervals (e.g., 40 hours versus two hours), and these cases were removed from their overall statistical analysis. The multiple correlation coefficient was obtained for the degree of autolysis and their results suggested that the mode of death, temperature at the time of death, cause of death, and clinical conditions all need to be considered for those cases of unexpected autolysis for postmortem interval. The extent of autolysis was most significantly related to the postmortem interval. With respect to mode of death, there was a statistical significance between acute and chronic death.

The pancreas has been investigated immunohistochemically as a tool in establishing the postmortem interval based on the immunoreactivity with antibodies to glucagon (36). The pancreas from 214 corpses (for which the time since death was known to be between one and 21 days $\pm$ one day from police investigations) were stained with antibodies to glucagon. The circumstances in which the bodies were recovered were all different with respect to environmental parameters (e.g., site of discovery, temperature, and humidity).

It was demonstrated that pancreatic α -cells exhibited positive immunoreactions for glucagon in all cases up to six days old but no corpse older than 14 days exhibited a positive reaction. The interpretation was that a positive immunoreaction indicates a time of death less than seven days prior to postmortem examination and absence of glucagon immunoreactivity in the specimen indicated that the time of death must be at least 13 days earlier. However, a negative immunoreaction could occur earlier and a positive immunoreaction could occur later under different environmental conditions.

The differentiation of pancreatic autolysis from acute pancreatitis should be relatively straightforward with lack of an acute inflammatory response being one of the main discriminating features for autolysis (**Images 7 and 8**) and the presence of an acute inflammatory response pointing towards acute pancreatitis (**Image 9**).

The Pancreas in Diabetes Mellitus

Pathological changes in the pancreas are evident in both type 1 and type 2 diabetes mellitus. Type 1 diabetes is a multifactorial disease that develops from a complex interplay of host genetics, the immune system, and the environment with resultant destruction of the insulin-producing beta cells of the islets of Langerhans.

Image 7: A) Mild autolysis (H&E, x20) and **B)** (H&E, x400).

Islets in the commonly sampled body and tail of the pancreas contain four main endocrine cell types. Approximately 80% of the cells are insulin-secreting β cells, 15% glucagon-secreting α cells, 4% somatostatin-secreting δ cells, and 1% contain pancreatic polypeptide (PP) (37).

The presence of insulinitis in the islets of the pancreas of a predominantly lymphocytic inflammatory infiltrate was reported in the 1965 seminal article by Willy Gepts who had identified it in 68% of autopsies (15 of 22 persons) performed on decedents who were under

the age of 30 years and had died within six months of a diagnosis of diabetes (38). A larger collection of samples in the UK confirmed these findings, where 47 out of 60 (78 %) of young patients under the age of 20 years were found to have insulinitis (39).

Gepts had also noted that the pancreas in persons who had been afflicted with the disease for many years was characterized by an almost complete lack of insulin-secreting beta cells, and this was reported before the advent of immunohistochemistry. Two hypotheses for the islet cell inflammation flowed out of this,

Image 8: Severe autolysis of the pancreas **A)** (H&E, x10) and **B)** (H&E, x400).

Image 9: Acute pancreatitis **A)** (H&E, x100) and **B)** (H&E, x200).

namely that the islet inflammation could be secondary to a viral infection of beta cells, or could represent an autoimmune process.

Support for both theories was obtained when it was shown that patients with recently diagnosed type 1 diabetes were more likely than controls to have antibodies to Coxsackie viruses (40), and Coxsackie B4 virus was cultured from the pancreas of a 10-year-old boy who had died at clinical presentation of type 1 diabetes (41). As the virus was also cultured from the brain of the child, it was stated that this case may have been exceptional in that there was a possibility of an incidental viremia. In 1974, two separate groups reported the presence of islet cell autoantibodies in patients with type 1 diabetes (42-44), which led to a subsequent reclassification of the disease as an organ-specific autoimmune disease that targeted the insulin-secreting beta cells of the islets.

The use of immunohistochemistry on paraffin-embedded tissue has shown that most islets (70%) were small and had no beta cells in children dying at clinical presentation of their disease (45). However, a normal complement of glucagon-secreting alpha cells, somatostatin-secreting delta cells, and pancreatic polypeptide-secreting PP cells were identified and these cases were termed insulin-deficient islets (IDI). The remainder of the islets had residual beta cells and were called insulin-containing islets (ICI). Insulinitis affected 18% of ICI but only 1% of IDI, which provided the first evidence that insulinitis affected ICI primarily and lent support to the idea that it represented an immunologically driven destruction of beta cells (45). Importantly, a lobular distribution of the disease was also noted, where a seemingly unaffected lobe, or one where ICI with insulinitis could be observed, was frequently surrounded by lobes containing only IDI.

Histological examination of the pancreas in decedents with long-standing type 1 diabetes mellitus will essentially reveal an absence of β cells; however, there will be a normal number of islets containing normal numbers of α , δ , and PP cells (39).

In well-developed insulinitis, lymphocytes outnumber macrophages by ten to one, and there are more T cells than β cells (46). CD8 T cells outnumber CD4 cells (47). In most cases, there are islets which appear histologically normal and contain normal numbers of endocrine cells, and are not inflamed. These three populations of islets, therefore, represent examples of islets before, during, and after destruction of β cells in the insulinitis process.

The pancreas in middle-age-onset and early-age-onset type 2 diabetics will contain lesions in the islets and exocrine pancreas (48). The lesions of the exocrine pancreas are represented by stromal inflammatory changes, atrophy of the acinar tissues, interstitial fibrosis of lobules, fatty infiltration of the lobules and interlobular areas, arteriosclerotic changes of nutrient arteries, and ductal lesions. Ductal lesions are represented by obstruction or dilatation, with or without epithelial hyperplasia with the possibility of transformation into dysplastic changes. Vascular abnormalities can consist of atherosclerotic and hyaline changes with associated narrowing of lumina.

Although the pathological changes in the pancreas in middle-age-onset diabetes mellitus have been well known for years, the pathological findings of the pancreas in early-onset type 2 diabetes mellitus were only first characterized in 2017. The salient features identified were marked atrophy of the pancreatic parenchyma, ductal obstruction or dilatation (with epithelial hyperplasia) and dysplasia, interstitial fibrosis, fat infiltration, reduction of volume and mass of the β cells, and marked amyloid deposition in the islets.

Although it is generally accepted that pancreatic atrophy is common in type 1 diabetes mellitus (49-51), it is still controversial in middle-age-onset type 2 diabetes mellitus (52-54).

Pancreatitis

Inflammation of the pancreas (pancreatitis) can develop as an acute phenomenon (acute pancreatitis) in response to a variety of parenchymal insults (e.g., alcohol, gall stones, trauma, drugs, scorpion stings,

hypothermia) or can be recurrent, chronic, and relapsing (chronic pancreatitis). Acute pancreatitis has been dealt with in the accompanying article on the topic (55) and will not be dealt with further here, except to remark on the gross appearance of lipolytic fat necrosis, which is most times apparent as focal chalky white spots of saponification in the omentum and mesentery on opening the abdominal cavity (**Image 10**).

Chronic Pancreatitis

Chronic pancreatitis is characterized by the persistent and relentless progression of pancreatic lesions with diverse manifestations and complications (56). It is these characteristics that distinguish chronic from acute pancreatitis, the latter of which usually resolves on removal of the causative insult.

Chronic pancreatitis can develop in the setting of chronic alcoholism, protein energy malnutrition (PEM), ductal obstruction, hyperparathyroidism, renal transplantation, and mucoviscidosis, but can also be of unknown etiology (i.e., idiopathic chronic pancreatitis). Chronic alcoholism is the most common cause of chronic pancreatitis in the western world.

The natural history of chronic pancreatitis is punctuated by recurrent episodes of painful acute pancreatic inflammation, the so-called relapsing or recurrent chronic pancreatitis. Possible complications that may develop include malabsorption; weight loss; diabetes mellitus; ascites and/or pleural effusion; narrowing of the common bile duct, duodenum, and/or colon; left-sided portal hypertension from thrombosis of the splenic, superior mesenteric, and/or portal veins; major arterial hemorrhage; and chronic pain.

Image 10: Chalky spots of fat necrosis (saponification) (arrows) of the mesentery in a case of acute pancreatitis.

The pathological features of chronic pancreatitis and acute pancreatitis were discussed at the Second International Symposium on Pancreatitis at Marseilles (57). The inflammatory process of chronic pancreatitis is initially directed at the exocrine tissue, which is destroyed first and then followed by destruction of the islets of Langerhans. However, the functional reserve capacity of the pancreas is so great that clinically significant pancreatic insufficiency does not occur until more than 85% of functioning tissue is lost, and only then the clinical sequelae of malabsorption, steatorrhea, and insulin-dependent diabetes will ensue.

Pathologically, established chronic pancreatitis is defined by the combination of fibrosis, parenchymal atrophy, and ductal pathology (**Images 11 A to F**). In the early stages of the disease, the pancreas may be normal but will become firm later on. Its surface may be pink or grey-white and its lobulated appearance will disappear in the most severely affected areas, with a white appearance and little or no bleeding on sectioning of the tissue (58). The main pancreatic duct may be segmentally dilated or exhibit a spiral or corkscrew appearance along its entire length. Grossly evident atrophy of the pancreas occurs in the final stages of disease evolution when the gland is often noticeably shrunken and hardened.

Microscopically, precipitation of proteinaceous material within the lumina of the intercalated and canalicular ductules, from supersaturation of protein enzymes in the pancreatic juice of chronic alcoholics, is the earliest change that is evident. Mineralization of the precipitated proteinaceous material is facilitated by secretion of ionized calcium into the pancreatic juice to give rise to the characteristic “calcification” that develops on progression of the disease (**Image 11A**). Variable chronic inflammatory cell infiltration of the interstitium occurs in association with progressive, destructive loss of acinar tissue and the deposition of/replacement by dense fibrous tissue near ducts and within and/or between lobules (**Images 11B to E**). In established disease, the parenchyma is wholly replaced by fibrous tissue punctuated by a few nests of acinar tissue and some resistant residual islet cells. It is unclear why the islet cells persist in this prolonged

inflammatory process and survive the longest. It has been postulated that their extremely rich blood supply makes them more resistant to ischemia (56). Despite their persistence, it must be noted that affected individuals will still develop diabetes mellitus despite the “normal” appearance of the islets with another postulate being that the surrounding fibrous tissue prevents entry of the blood sugar regulating hormones into the circulation by occluding small venules (56).

From an etiological perspective, chronic pancreatitis can be broadly categorized into that due to chronic alcoholism (aCP) and that due to obstruction of the pancreatic ductal system, the so-called obstructive chronic pancreatitis (oCP). These two broad categories of chronic exhibit distinct and differentiable pathological features (56).

In alcoholic chronic pancreatitis, a lobular distribution of lesions is evident with features of both obstruction from protein plugs and dilatation of the canalicular and intercalated ducts (56).

The precipitation of protein plugs in the ductal system of the pancreas of alcoholics is very likely a result of an increase in concentration of the protein content of pancreatic juice, since the pancreatic juice of alcoholic patients is supersaturated with enzyme protein (58, 59). A glycoprotein of 13 500 daltons was isolated from calculi in ten patients with chronic pancreatitis (59-61). The initial component of the protein plug is believed to be the constituent proteins in pure pancreatic juice but the isolated glycoprotein predominates later. Calcium carbonate (calcite) is progressively added to result in the characteristic calcifications seen histologically. Enhanced secretion of calcium ions into the pancreatic juice may facilitate the process (62). Alcohol may cause most of its damaging effects by creating multiple points of ductal obstruction from precipitation of these protein plugs (63). Small, rounded ductular cavities lined by cuboidal epithelium are commonly seen in association with the ductular obstruction and contain either pure pancreatic juice, semi-digested debris and necrotic material, or blood (64). Ductular proliferation proximal to the points of obstruction is thought to be responsible for the fore-

Image 11: Chronic pancreatitis, **A)** Calcified luminal protein precipitation in a ductal lumen (H&E, x40), **B)** With marked parenchymal loss and interstitial replacement fibrosis (H&E, x50), **C)** Acinar atrophy with replacement fibrosis (H&E, x50), **D)** Cystic dilatation of ducts and interstitial replacement fibrosis with mononuclear inflammatory cell infiltration (H&E, x50), **E)** Marked lymphocytic chronic inflammatory cell infiltrate within fibrosis tissue (H&E, x400), **F)** Chronic pancreatitis – dilated duct with luminal debris (H&E, x50), **G)** Chronic pancreatitis – higher power magnification of the interface of a dilated duct (H&E, x400).

going pathology, which constitutes one of the earliest responses to injury (65). The precipitated protein plugs result in ductular dilatation, which is followed by acinar atrophy. A variable inflammatory infiltrate may develop in the interstitium and considerable fibrous tissue is laid down near the ducts and within the lobules. Disappearance of parenchymal tissue occurs with associated progressive replacement by dense fibrous tissue, which often contains scanty inflammatory cell infiltrates (**Image 11E**). The ducts can be either widely dilated or normal. Dilatation of the ducts may be the consequence of occlusion of their lumina by protein plugs in the early stages of the disease, calculi in the late stage, or by traction of adjacent fibrous tissue brands on the outside of the duct walls to give rise to pseudosacculations. In the final stage of the disease, the pancreas is replaced by fibrous tissue with only a few nests of acinar cells and some resilient islet cells remaining. Again, it is unclear why the islets cells persist and survive the longest and it has been postulated that their extremely rich blood supply makes them more resistant to ischemia (56).

Nakamura and colleagues investigated and demonstrated the development, enlargement, and progression of intraluminal protein plugs in chronic pancreatitis with incorporation of calcium carbonate, desquamated epithelium, and intraductal debris by creating three-dimensional profiles of the pancreatic ducts (from the secondary branches through to the terminal acini) by examining serial sections of pancreatic biopsies from patients with chronic pancreatitis, duct obstruction secondary to a small tumor, and from a patient within normal pancreas (66). They showed the calculi were composed of various proteins with a so-called “stone protein” of around 13 000 daltons predominating. Phosphorous and magnesium accounted for less than 5% of their dry weight and sodium less than 0.5%. In cross-section, the calculi contained amorphous centers with progressive concentric layers of calcification being laid down from the outside inwards. All stages of evolution of pancreatic calculi were seen, ranging from the initial proteinaceous plugs to fully formed stones. The mature calculi varied considerably in size, shape, and weight.

In contrast, obstructive pancreatitis is rarely associated with intraductal precipitates with the small ducts often having a normal appearance but with more widespread damage of the exocrine component.

Many investigators stressed that alcoholic chronic pancreatitis was a pathologically distinct entity which can be differentiated from obstructive pancreatitis, with the cardinal features of differentiation being a lobular distribution of lesions, alterations of the intralobular ducts (i.e., dilatation and epithelial atrophy), frequent protein plugs within the ductal lumina, perineural inflammation, and nerve changes as occurs in alcoholic chronic pancreatitis (**Table 1**) (67-69).

The pathological changes of oCP are well described. Obstruction of the pancreatic ductal system can arise from multiple causes that include fibrosis of the ampulla of Vater, papillary inflammation, strictures of the main pancreatic duct (congenital or acquired), and tumors. The macroscopic features of oCP are similar to that of aCP but with markedly different microscopic features. The lesions of obstructive pancreatitis are diffuse and lack a lobular topography with no sparing of the exocrine component of the pancreas. The major ducts maintain a regularity of their caliber with no alternating segments of stenosis and dilatation, but being moderately dilated, with the smaller branches being of normal caliber. The ductal epithelium is intact with empty ductal lumina and rare protein plugs and calcifications (70).

Pancreatic Changes in Hypothermia

Historically, a variety of changes in fatal hypothermia have been described in the medical literature between 1940 to present day and consist of acute inflammation, hemorrhages, and optically-clear cytoplasmic vacuolation of the pancreatic acinar cells (**Image 12**), with a variable reported frequency of between 10-73% (71). No explanations for the pathogenesis of these changes are known.

In 1943, Muller et al. first reported on numerous, fine, granular, non-fatty vacuoles of variable frequency in the protoplasm of pancreatic acinar cells (72, 73), and

Table 1: Comparison of Alcoholic Chronic Pancreatitis and Obstructive Chronic Pancreatitis

Feature	Alcoholic Chronic Pancreatitis	Obstructive Chronic Pancreatitis
Topography of lesions	Lobular distribution	Diffuse involvement (no sparing of exocrine tissue)
Duct morphology: Major ducts	Alternating segments of stenosis and dilatation	Moderately dilated but of regular caliber
Duct morphology: Intralobular ducts	Dilated with epithelial atrophy	Normal caliber. Intact epithelium
Protein plugs and calculi	Frequent luminal protein plugs	Empty lumina; rare protein plugs and calcification
Perineural inflammatory infiltration	Present	Absent

Image 12: Cytoplasmic vacuolation of pancreatic acinar cells (H&E, x400).

this finding was re-reported by Gillner and Waltz in 1971 who had also identified them in epithelial cells (74). However, it must be noted that Buchner, in another study, did not find any pathological changes in the pancreatic islands (75).

In their 2007 publication on their review of 143 cases of fatal hypothermia in which microscopic examination of the pancreas had occurred in 62 cases, Preuss et al. identified 24 cases (38.7%) with optically empty vacuoles of the adenoid cells (71). The vacuoles were located adjacent to the well-circumscribed nuclei, frequently in the basal parts of the cells. A control group of 25 non-hypothermia cases was also examined and no vacuoles were identified.

They concluded from the analysis that hemorrhage and inflammation of the pancreas cannot be regarded as reliable signs of death from hypothermia since bleeding was identified in both cohort and control groups. Only cytoplasmic vacuolation of pancreatic acinar cells appeared more frequently in hypothermia. Vacuolations were not found in either of the control groups, with or without a history of alcoholism. However, they were observed in connection with signs of chronic pancreatitis. Similar findings were described by Gillner and Waltz. Their pathogenesis is postulated to be along the lines of the general hypoxia akin to deaths that occur at high altitude (74). An alternative explanation that has been offered is that the vacuoles in the pancreatic acinar cells reflect impaired pancreatic secretion as a manifestation of the pre-stage of dyschylia, with the secretory pancreatic granules remaining in the acinar cells because of impaired exocytosis instead of being excreted into the pancreatic duct.

Gedigk's textbook of pathology in 1990 stated that every dysfunction of the metabolism of the adenoid cells from hypoxia, hypothermia, or toxic damage resulted in a decrease or loss of the permeability barrier of the cells with the loss of protection against auto digestion (76). The permeability barrier ensured that the enzymes did not infiltrate the cytoplasm of the acinar cells. He stated that enzymatic auto digestion of the acinar cells because of impaired permeability is the cause of acute pancreatitis. However, cytoplasmic

vacuolation of acinar cells was not described by him as a morphological sign of pancreatitis. Since subclinical acute pancreatitis was observed by other authors in fatalities with heavy shock or pronounced circulatory depression, they concluded that the changes in the acinar cells or pancreatic duct system are the result of hypoxia (77). As such, the cytoplasmic vacuoles of the pancreatic acinar cells are either vesicles filled with enzymes that could not be secreted because of impaired exocytosis or autophagic vacuoles on the base of an impaired permeability of the acinar cells, or fatty degeneration from hypoxia (76, 77).

Preuss et al. reported that microscopically observable, optically empty cytoplasmic vacuoles of the pancreatic acinar cells from impaired exocytosis have been known as a sign of chronic alcoholism for years and are associated with leukocytic infiltration and fibrosis (71). Since they identified optically empty vacuoles in 38.7% of their cases of hypothermia in the absence of other signs of chronic pancreatitis, the presence of the vacuoles was interpreted as an additional sign of hypothermia. However, the content of the vacuoles in hypothermia remains unanswered and further investigations are needed. They were certain that macroscopic or microscopic hemorrhage and inflammation can be ruled out as part of the diagnostic criteria for fatal hypothermia.

Cytoplasmic vacuolation of the cells of the anterior pituitary gland has also been described in hypothermia (78, 79).

Tumors of the Pancreas

Both benign and malignant tumors of the pancreas can develop in either the exocrine or endocrine components.

Adenocarcinomas of the pancreas are relatively infrequent in the practice of forensic pathology as most times the diagnosis is well known after it has been clinically established and result in a natural cause and manner of death. Most times, these cases do not come to the attention of forensic pathologists and, as such, malignant neoplasms of the pancreas do not usually

present for postmortem examination unless there is some peripheral medicolegal issue which has arisen related either to the diagnosis and/or treatment of the lesion. Therefore, the forensically relevant neoplastic lesions of the pancreas consist of physiologically active tumors of the endocrine portion of the gland, more so those that secrete insulin.

Endocrine tumors of the pancreas account for 1 to 2% of all pancreatic neoplasms (80).

They were formerly known as islet cell tumors but this term is only properly applied to tumors composed of cells normally present in the pancreatic islets (i.e., insulin, glucagon, somatostatin, and pancreatic poly-

peptide) and pancreatic endocrine tumor (PET) is the preferred more generic name (81, 82).

They may also be referred to as pancreatic neuroendocrine tumors (PanNET or PNET), which are neuroendocrine neoplasms arising from cells of the endocrine and nervous system within the pancreas (**Images 13 and 14**).

Functional tumors associated with secretion of a relevant hormone are classified according to the hormone produced (e.g., insulinoma, glucagonoma, somatostatinoma, or vipoma) and the related endocrine syndrome. This is also applicable to neoplasms associated with syndromes from hormones produced by

Image 13: Encapsulated pancreatic endocrine tumor (H&E, x50).

cells which are ectopic to the adult pancreas such as gastrin, adrenocorticotrophic hormone, serotonin, or growth hormone releasing factor. Pancreatic endocrine tumors not associated with distinct hormonal syndrome are otherwise classified as nonfunctioning. Sixty to eighty five percent of pancreatic endocrine tumors are functional as determined in a large series of surgically removed tumors, with insulinoma being the most frequent subtype, accounting for up to 70%, followed by gastrinomas (80, 82-84). Approximately 15 to 25% of all pancreatic endocrine tumors may be associated with multiple endocrine neoplasia type 1 (MEN-1).

The threshold diameter for grossly evident tumors is 0.5 cm and tumors below this size are considered microadenomas (85). The occurrence of multiple microadenomas of the pancreas may be seen in MEN-1 syndrome. Multiple endocrine neoplasia type 1 is an inherited predisposition to tumors of the anterior pituitary, parathyroid glands, pancreas, duodenum, and occasionally in the stomach, ileum, lung, and thymus (86-88). The *MEN 1* gene is a tumor suppressor gene that codes for a protein called menin (89).

The prevalence of pancreatic endocrine tumors is estimated to be less than one in 100 000 and the incidence rate is deemed to be substantially lower because of the inherently more favorable prognosis generally (90).

Image 14: Pancreatic endocrine tumor (H&E, x50).

Functional insulinomas will result in hyperinsulinemic hypoglycemia, which can prove to be fatal and needs to be differentiated from the exogenous administration of insulin. Classically, patients with functional insulinomas and hyperinsulinemic hypoglycemia will present with a history of mental confusion, weakness, fatigue, and seizures whilst fasting, and blood glucose concentrations below 50 mg% with immediate resolution of their symptoms following ingestion of glucose, which constitutes the so-called “Whipple triad” (91). Analysis of serum extracted from postmortem blood for insulin and C-peptide will reveal elevated concentrations of both insulin and C-peptide in an approximately 1:1 ratio, in contrast to exogenous administration of insulin in which the concentration of insulin will be many times greater than the concentration of C-peptide. Given that many tumors are microadenomas, it may be impossible to identify the location of the tumor in the pancreas, duodenum, or elsewhere even on diligent examination and serial sectioning. In the absence of a grossly or microscopically identifiable insulinoma, it is the ratio of insulin to C-peptide that will establish the postmortem diagnosis that a functional insulin-secreting endocrine neoplasm was responsible.

Functional gastrinomas result from the inappropriate secretion of gastrin and give rise to the clinical Zollinger-Ellison syndrome (ZES), which is characterized by gastric acid hypersecretion, intractable peptic ulceration, and occasionally severe diarrhea (92, 93). Zollinger-Ellison syndrome is sporadic in 60 to 75% of cases with the remainder being a manifestation of MEN-1 syndrome.

The clinical manifestation of glucagonoma syndrome results from the catabolic action of excessively elevated glucagon concentrations (94) and consists of weight loss, mild glucose intolerance, depression, normochromic normocytic anemia, a tendency to develop deep vein thrombosis, and a skin rash known as necrolytic migratory erythema (95). It has not been described in extra-pancreatic glucagon producing tumors.

The Verner-Morrison syndrome results from the excessive secretion of vasoactive intestinal polypeptide (VIP) by VIPomas and is defined by watery diarrhea, hypokalemia, and achlorhydria (WDHA) (96).

An additional, less well defined syndrome results from the widespread inhibitory effects of somatostatin when produced by a pancreatic endocrine tumor and consists of diabetes, cholecystolithiasis, steatorrhea, indigestion, hypochlorhydria, and occasional anemia (97, 98).

Other rare endocrine syndromes are infrequently observed with pancreatic endocrine tumors from ectopic hormone production by tumors of the pancreas and can be due to the production of adrenocorticotrophic hormone (ACTH) in Cushing syndrome, serotonin (a typical carcinoid syndrome), growth hormone releasing factor (acromegaly), and parathyroid hormone (PTH) in paraneoplastic hypercalcemia (99-104). Combinations of various hormonal syndromes or transitions have been described but are extremely rare.

Nonfunctional endocrine neoplasms of the pancreas tend to become clinically apparent from symptoms associated with their large size, invasion of adjacent organs, or the development of metastases. The relevant history will be of abdominal pain, jaundice, and weight loss. Infrequently, they may present as pancreatitis (105) or in association with hematologic abnormalities or eosinophilic infiltration of the skin (106, 107).

Pancreatic endocrine neoplasms are potentially malignant and the rate of malignancy varies amongst the different tumor types. Insulinomas have the lowest incidence of malignancy of only 5-15% (90, 108), whereas 60-85% of the other tumor types, inclusive of nonfunctioning tumors, are malignant (109).

In general, malignant metastasizing pancreatic endocrine tumors are slow-growing indolent neoplasms with survival from the time of diagnosis usually being in the range of two to ten years. Metastasizing gastrinomas arising in the pancreas carry a shorter survival compared to those arising in the duodenum (110, 111).

CONCLUSION

The spectrum of traumatic and natural disease pathology that can affect the adult pancreas is multiple and varied. The more commonly encountered entities have been presented from both pathological and pathophysiological perspectives. Acute pancreatitis has not been dealt with since it has been specifically addressed in a separate article in this issue (55). Although many of the conditions are extremely rare and may never be encountered in the professional lifetimes of an individual pathologist, forensic pathologists still need to be aware of them in case they are one day faced with these entities as possible diagnoses at autopsy because of clinical concerns raised in life or to explain unexpected biochemical results and unexpected deaths.

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