The pancreas : its surgery and pathology / by A.W. Mayo Robson and P.J. Cammidge.

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THE PANCREAS

ITS SURGERY AND PATHOLOGY

BY

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PREFACE

Our present knowledge of the physiology, pathology, and surgery of the pancreas, like so many other advances in medicine in recent years, was rendered possible by the beneficent work of Lister. So long as clinical observation was only capable of being checked by the experience of the post-mortem room, and by an occasional accidental experiment on the living subject, the important and complex part that the pancreas plays in the physiology of the body remained unsuspected, and descriptions of the diseases to which it is liable were confined to a few lines on malignant disease, cysts, and calculi. Animal experiments, now rendered safe by antiseptic surgery and improved technique, have thrown a flood of light on the physiology of the organ and elevated it from the position of a mere accessory digestive gland to the rank of a structure indispensable for the metabolic needs of the organism. The numerous laparotomies undertaken in recent years have afforded the surgeon opportunities of observing and handling the living organ, both in health and disease, and a comparison of the conditions noticed, together with a closer investigation of the symptoms and after-histories of the cases, has very considerably widened our conception of the pathological changes that may occur in the gland and afforded a basis for their clinical differentiation. Histological and post-mortem inquiries, stimulated by the impetus thus given, have still further increased our knowledge, and confirmed the conclusions of the bedside and the operating theatre. There are as yet many points on which observers are not agreed, and there are questions

which still call for elucidation, but the enormous literature of to-day as compared with that prior to 1886, when Professor Senn of Chicago published his valuable experimental work on the pancreas, shows the great advances that have been, and are being, made in the subject.

The symptomatology and pathology of the pancreas are so intimately bound up with the physiology and anatomy of the gland, and these again are rendered so much more easily understood if the comparative anatomy and development of the organ are borne in mind, that we have prefaced the pathological and clinical sections of this work with a brief, but we hope sufficiently comprehensive and accurate, account of those subjects.

In the chapter on histology, and again later under the heading of diabetes, we have discussed the structure and supposed functions of those characteristic groups of cells known as the islands of Langerhans. In doing so we have endeavoured to impartially summarise the evidence for and against the contending views that are held with regard to them, but, as will be gathered from the text, we personally are of opinion that the balance of available evidence strongly points to their being independent structures related to the control of carbohydrate metabolism within the body that the pancreas undoubtedly exerts.

A thorough comprehension of the chemical changes induced in the body by diseases of the pancreas would include a knowledge of the pathology of diabetes, but at present we are still in the dark as to the true essentials of that condition. Our description of the chemical pathology of the pancreas is therefore largely confined to the condition of the urine and fæces found to accompany disease of the gland, and although we have now devoted special attention to this subject for six or seven years, we are conscious that as yet only the fringe has been touched upon. The so-called "pancreatic" reaction in the urine is still under investigation. The improved

method described in these pages is undoubtedly a distinct advance on the original process described in the Arris and Gale lecture of 1904, but it is not yet as perfect as it might be. The difficulty of the investigation is considerable, for the quantity of material to be obtained from any one case, even when a well-marked reaction is given, has proved to be small, and it is only by collecting very large amounts of urine from suitable cases, whenever they have occurred, that we have been able to make slow advances. We do not consider that at present we are in a position to make more positive statements than those expressed in the chapter on chemical pathology, but we hope that we may shortly be able to do so. In our own practice we never rely upon the "pancreatic" reaction alone in making a diagnosis of pancreatitis or malignant disease of the pancreas, but always take into account the results of a complete analysis of the urine and a chemical examination of the fæces, as well as the clinical symptoms; it is from neglect of these precautions, and under the false notion that the "pancreatic" reaction was claimed to be pathognomonic, that the mistakes made by some writers have arisen. The examination of the fæces often gives important confirmation of the presence or absence of disease of the pancreas, but this is not always the case, and the possible causes of unexpected results described in the text have always to be borne in mind. The question of the cause of the absence of colour in the stools in various pathological conditions has excited attention for many years, and, although we do not suggest that the explanations our investigations and observations have enabled us to make are true of all cases in which the fæces are white, they appear to be so for pancreatic disease.

There seems to be an impression in the minds of nearly all members of the profession that diseases of the pancreas, excepting some of the grosser lesions, are unrecognisable during life, but we venture to think that a careful

perusal of the chapter dealing with general symptomatology and diagnosis will show that while no single sign or symptom is characteristic of disease of the pancreas, no more than of any other organ, the cumulative evidence to be obtained by a careful investigation of the history, clinical symptoms, and signs, and the indications to be obtained by the methods of the laboratory, should leave no doubt as to the presence or absence of pancreatic trouble in any particular case and, in the large majority, allow of a definite opinion as to the nature of the lesion being arrived at.

The classification of inflammatory lesions of the pancreas is the same as that outlined in the Hunterian Lectures of 1904. Increased experience has only served to demonstrate its clinical utility, and its adoption by subsequent writers shows that they recognise the numerous forms that inflammation of the pancreas may assume under various conditions. We have emphasised the intimate etiological relation existing between gall-stones and pancreatitis and pointed out the conditions under which biliary calculi in the common bile-duct are likely to cause, and will fail to give rise to, pancreatic inflammation. We have also laid stress upon the no less important, but less commonly recognised, association of inflammation of the pancreas with catarrhal conditions of the upper part of the gastro-intestinal tract. Pancreatitis resulting from a duodenal catarrh may, under certain conditions, give rise to more or less persistent jaundice, and, in our experience, is the most common cause of the conditions usually known as acute and chronic "catarrhal" jaundice.

In dealing with the subject of diabetes we have devoted much space to a consideration of its relations to the pancreas, and have quoted the more important experimental evidence and clinical work bearing upon the subject. Between the ofttimes conflicting, and even contradictory, statements of different authors it is difficult to arrive at

any very definite conclusions as to the frequency of pancreatic lesions in diabetes and as to how these are related to the disease, but one fact that has been clearly established is that a small portion of normal gland is capable of averting the onset of the condition. It is therefore important that diseases of the pancreas should be recognised at the earliest possible moment, and that conditions likely to give rise to pancreatic lesions should be radically treated before they have had time to bring about permanent, and may be progressive, injury of the gland. For this reason we strongly advocate the early treatment of gall-stones, especially when they are present in the common duct and an examination of the urine and fæces shows that a pancreatic lesion exists. The very striking increase in the death-rate from diabetes shown by the Registrar-General's returns is possibly not unconnected with the greater prevalence of digestive disturbances in recent years, and we therefore think that duodenal catarrh and the frequently associated catarrhal pancreatitis always call for prompt attention.

One of the most important practical results that has followed from modern observations on the pancreas is the recognition of the very close similarity of the symptoms of cancer and chronic pancreatitis in the head of the gland. Many cases of the latter have in the past been allowed to die unoperated on, under the mistaken impression that they were suffering from cancer, and our experience would suggest that, even at the present time, there are many who do not realize the importance of a differential diagnosis between the two conditions. We have dealt with this subject under the headings of chronic pancreatitis and cancer, and it is also referred to in the chapters on pathology and symptomatology.

While a considerable number of the illustrations in this work are original and have been taken from preparations in our own possession, we are deeply indebted to

the various museums mentioned for permission to have drawings or photographs made from their specimens. Our thanks are also due to the authors and publishers, to whom acknowledgments are made, for the pictures appearing above their names.

To the end of each chapter we have appended a list of the more important papers and publications bearing on the subjects therein discussed. These do not make any pretense at completely exhausting the bibliography, but as a rule merely represent an alphabetical list of the authors mentioned in the text. In writing this work we have laid under contribution all the monographs available to us, as well as those papers that have appeared on the subject in the current literature. We have endeavoured as far as possible to credit each author with the views and cases of which he has written, and are particularly indebted to Opie, Oser, Rolleston, and Flexner. A certain number of illustrative cases and illustrations have also been taken from a work on "Diseases of the Pancreas" by A. W. Mayo Robson and B. G. A. Moynihan (Saunders & Co.), which has been for some time out of print. Each case and opinion has, as far as possible, been attributed to its original author, but should we inadvertently have misrepresented any of the writers quoted, or attributed a view or opinion to some other than its original author, we crave forgiveness and ask for correction.

A. W. Mayo Robson.
P. J. Cammidge.

London, *August, 1907.*

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THE PANCREAS

ITS SURGERY AND PATHOLOGY

CHAPTER I

COMPARATIVE ANATOMY

In unicellular organisms all the activities of life are embraced within the compass of a simple unit of living matter; it moves by contracting its substance, it draws back from hurtful influences, it absorbs oxygen, it engulfs and digests food, and gets rid of the waste products of its metabolism. But, early in the communal life of the multicellular metazoa, a tendency is seen to limit the physiological activities of the groups of cells, and to concentrate special functions in particular areas. As we advance up the scale of life this tendency becomes more and more marked, and these aggregations of cells, set apart to subserve particular purposes in the economy of the body, are differentiated as distinct organs. The more complicated and active the life of the animal, the more numerous are its organs, for, by the concentration of the activities of the cells on the performance of some special work, energy is economised, in the same way as division of labour in the commercial world is found to contribute to economy of production.

One of the most primitive areas to be set apart for the performance of a special function is that which deals with the absorption of food. First distinctly seen as a mere folding in of the surface to form a pouch, it assumes,

in most of the metazoa, the form of a canal passing through the tissues and connected with the external world by an apeture at either extremity. The cells lining the alimentary area, in its simplest form, show but little differentiation of structure, and, although they are predominantly digestive in character, they have not lost the primitive and many-sided qualities of the protozoön, as is shown by the ease with which a change of environment will bring about a change of function, so that those which were previously subsidiary become predominant. In the higher forms the characters of the cells become more fixed, their structure is modified to suit their special work and surroundings, and their power of reverting to the primitively complex physiological, but anatomically simple, type is lost.

Up to the echinoderms there is no indication of a particular concentration of the digestive powers in any one part of the alimentary tract. The walls may be pouched or ridged, to increase the surface, and one portion may be more muscular or harder than another, in order that the food may be better ground or mixed, but the whole extent of the tract is in contact with its contents, and no part is to be distinguished as especially set apart for the elaboration of digestive ferments. In a type such as the starfish, however, such glandular structures can be recognised. In this animal five branches are given off from the pyloric portion of the stomach, and each of these divides into two large digestive cæca. The glands themselves do not come into contact with the food, but secrete a ferment, which is said to have tryptic, peptic, and diastatic powers, thus showing the first definite step in the further differentiation of the functions of digestion and absorption.

Most of the Crustacea, Insecta, and Mollusca possess one or more pairs of similar digestive cæca, or glands, which join the alimentary tract in the region of the mid-

gut, or stomach. Their function is still complex, and no advance to a higher and simpler physiological type than that seen in the starfish is to be recognised.

In the lower members of the vertebrate series a similar state of things is found, and even in certain fishes the length of the intestine, a thickening of the mucous membrane of the duodenum, or the inactive nature of the species renders any special digestive glands unnecessary. In most osseous fishes, however, there is a well-defined gland having the characters and functions of a liver, and in addition an extension of the secreting surface of the intestine by the presence of a number of long, slender pouches, which are connected with the commencement of the duodenum. These differ in length and width, and, while the widest are sometimes found to be filled with the same contents as the intestine, the narrowest serve only as secreting organs, and are apparently specialised for the elaboration of digestive ferments. Their number and arrangement vary in different types. In the sand-lance there is only one, but in the whiting and salmon there are a hundred or more. In the herring, haddock, and salmon they are disposed in a line along the whole length of the duodenum, while in the whiting they are arranged in a circle around the distal end of the pylorus. A tendency to concentrate these intestinal outgrowths into a more typical glandular structure is seen in some

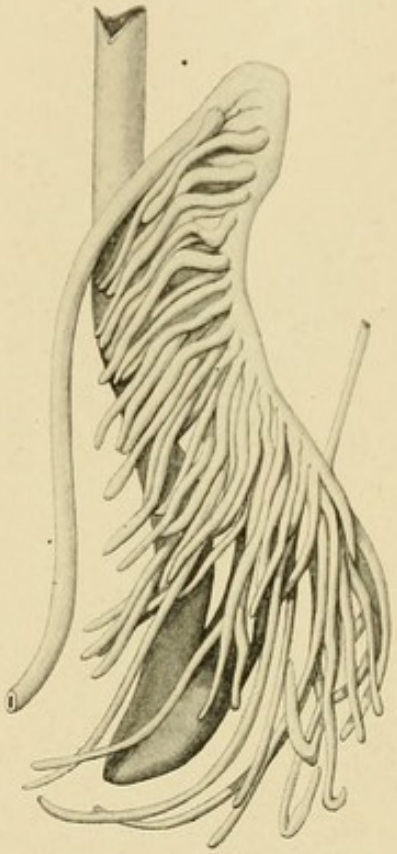

Fig. 1. — Pyloric appendages of the salmon (after Günther).

members of the class, especially in the more active types, in which rapid and complete digestion is a necessity. The 50 cæca of the pilchard open into the duodenum by 30 orifices, but the 120 of the whiting progressively unite into four or five groups, each communicating with the duodenum by a single duct. The swordfish has but two openings, and in the sturgeon a single wide duct terminates by a papilla on the internal surface of the duodenal wall, close to the ductus choledochus. The long, slender, ramified cæca are, in the two last, bound loosely together by connective tissue and possess a rich vascular supply, the whole being enclosed in a capsule, thus corresponding in structure to a conglomerate gland of the type of the pancreas. In many fishes that have typical pyloric cæca, and in some that do not possess these structures, there exists a conglomerate glandular organ opening by a duct into the duodenum, which is apparently the true homologue of the pancreas in air-breathing animals. A large-lobed structure of this description, the duct of which is so intimately connected with the bile-duct that both appear as a single structure externally, is found in the salmon. In the catfish it is very large, and the bile-duct passes through its substance. In the plaice, flounder, gar-pike, etc., it is situated in the mesentery and is smaller, but its duct in each instance accompanies the terminal portion of the ductus chole-

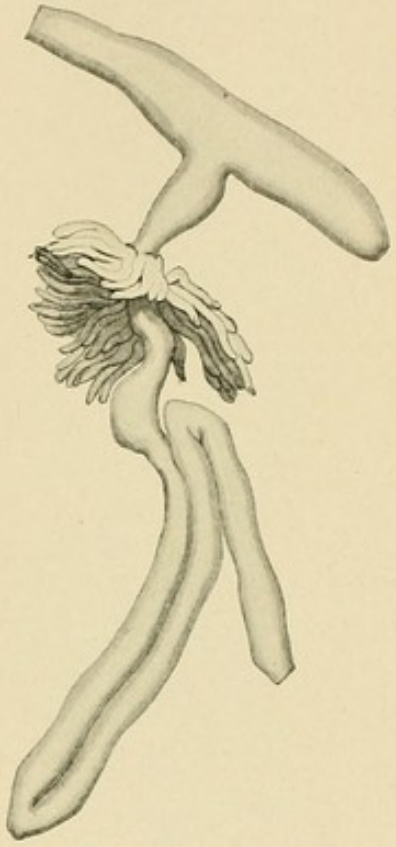

Fig. 2.—Alimentary canal of the whiting, showing the arrangement of the pyloric cæca (after Owen).

dochus. The characters of this organ in the sturgeon have already been referred to. A similar glandular mass of considerable size, lying behind the stomach, and close to the spleen, is met with in sharks and other elasmobranchs.

The liver in reptiles is proportionally large, and they

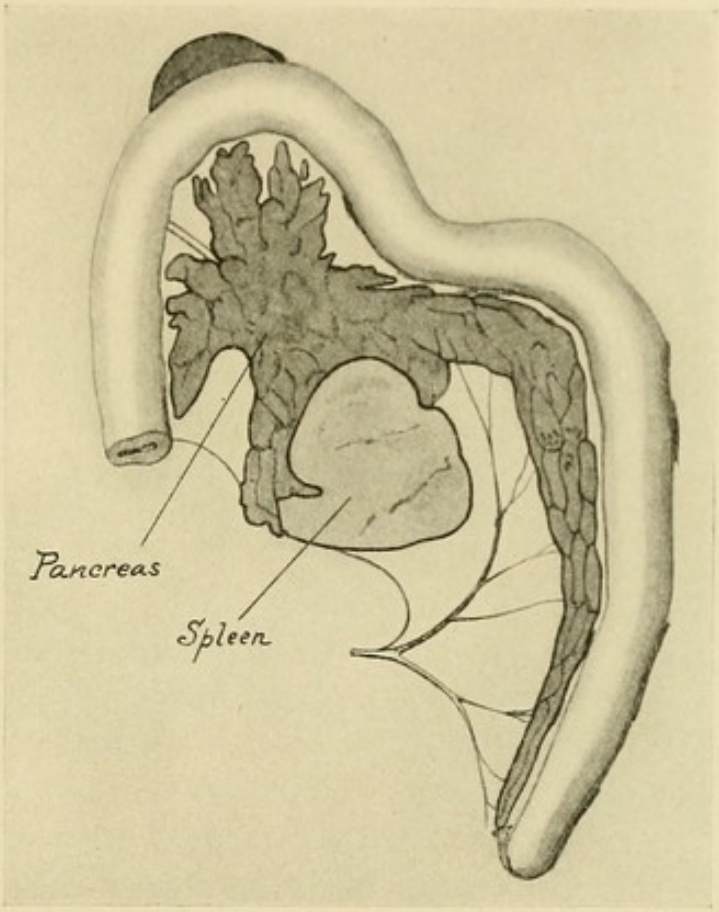

Fig. 3.—Pancreas and spleen of the turtle (after Owen).

possess a distinct and well-defined pancreas. The latter is a yellow or pink gland, consisting of many acini, each opening into a small duct. These ducts unite into larger ducts, and these again form a common channel, which opens into the intestine with, or close to, the bile-duct. The acini round the smaller ducts are aggregated

together to form lobules, and the lobules are again collected into lobes. In some members of the group the pancreas is spread out in the duodenal mesentery, but in most serpents and lizards it has a compact form; in the crocodile it is divided into two elongated lobes, and sometimes communicates with the duodenum by two distinct ducts; in the turtle the pancreatic duct terminates by a papilla opening into the expanded end or ampulla of the bile-duct. The pancreas of the carnivorous types of the reptilia is more bulky and compact, forming a larger proportion of the total weight of the animal than in the vegetable-feeders.

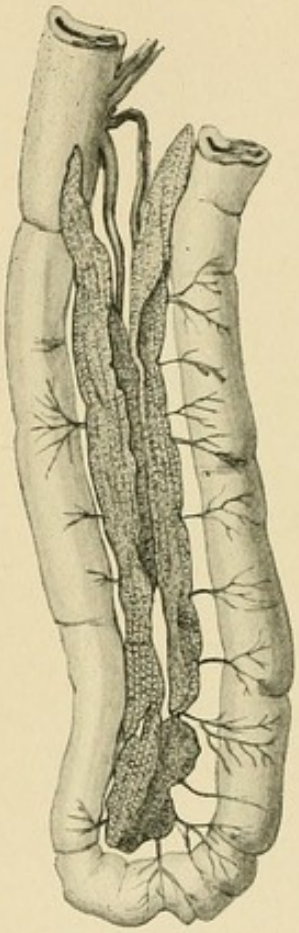

Fig. 4.—Pancreas and duodenum of goose (after Owen).

The pancreas of birds is usually firmer than that of reptiles. It is also relatively larger, probably to compensate for the absence of mastication and the salivary digestion of the food. It is long and narrow, lying in the space between the duodenal loops, and generally consists of two, and sometimes of three, portions. It communicates with the intestine by two, and occasionally by three, separate ducts, which open near the hepatic and cystic ducts.

In the mammalia the pancreas is more plainly of the conglomerate type. It is paler, and of a firmer structure, than in birds, and also differs by the development of a part, stretching towards the spleen, which is more or less distinct from that lodged within the duodenal loop. In the simpler members of the series, such as the marsupials, the gland is bent upon itself, running from the

duodenum to the spleen, behind the stomach, and giving off into the duodenal mesentery and omental folds more or less numerous processes. The main duct opens into the bile-duct, the bile and pancreatic secretion reaching the intestine through a common opening.

The main mass of the gland in rodents follows the curve of the duodenum, but sends numerous ramifying processes into the mesentery. The main duct, into which the minor

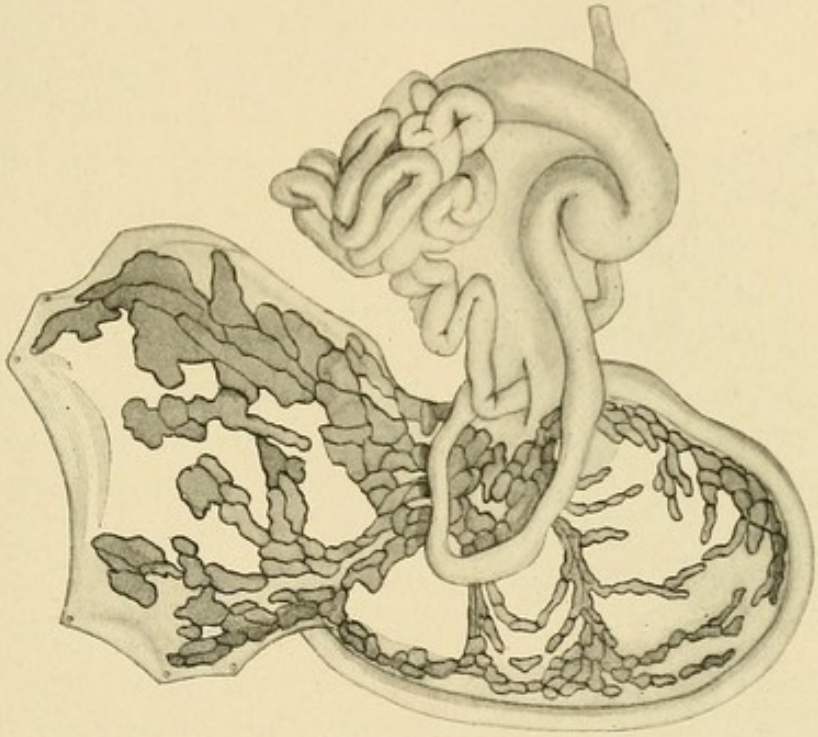

Fig. 5.—Pancreas of the rat (after Owen).

channels collect, enters the duodenum a considerable distance from the point of entry of the bile-duct. In the beaver 18 inches separates the papilla of the biliary passage from that of the pancreatic duct, and the latter is some 21 inches from the pylorus. A small, and usually impermeable, duct, corresponding to the main channel of the pancreas of most of the mammalia, can, in some instances, be made out joining the intestine in the neighbourhood of the biliary papilla. The functioning duct

in this group probably represents one of the lower members of the series of digestive cæca found arranged along the length of the duodenum in some fishes.

The pancreas of the aquatic mammals (Cetacea) is long, narrow, and compact. It crosses the spine at the root of the mesentery, the left end terminating near the spleen, and the right being expanded and adherent to the curve of the duodenum. The pancreatic duct joins the bile-duct.

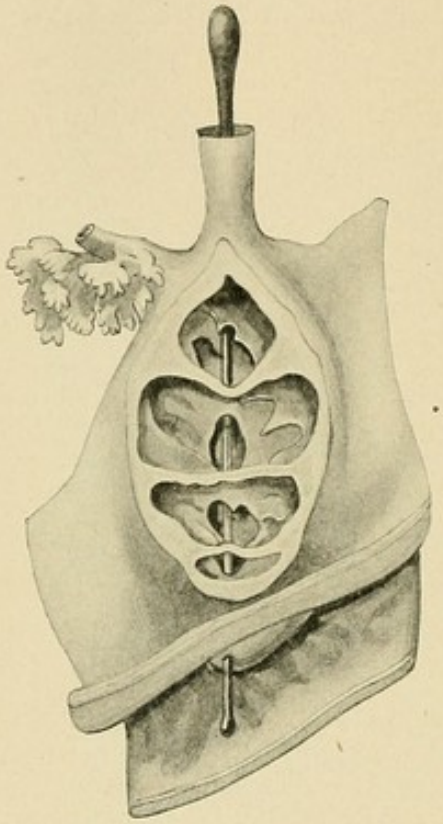

Fig. 6.—Terminal bile-pouch of the elephant, formed by the union of the common bile-duct and pancreatic duct (after Owen).

The transverse or splenic portion of the gland is still better developed in the ungulates, and, in this order, forms the larger part of the gland. Its duct, which is separate from that of the duodenal part, joins with the hepatic duct to form an ampulla before entering the intestine. The smaller, duodenal portion of the gland lies at right angles to the transverse part. It expands downwards and backwards in the duodenal mesentery. Its duct enters the duodenum about the same distance from the pylorus as the common bile and pancreatic opening, but by quite a distinct aperture.

The divisions of the pancreas in the ruminants are somewhat less well defined, the gland being broader and flatter in character.

The long, narrow pancreas of the carnivora shows a well-marked division into splenic and duodenal sections, which are of unequal length. The splenic part is straight

and runs transversely across the spine; the duodenal segment follows the curve of the duodenum. Both are covered by the peritoneum. In most members of the order the ducts of the transverse and descending portions anas-

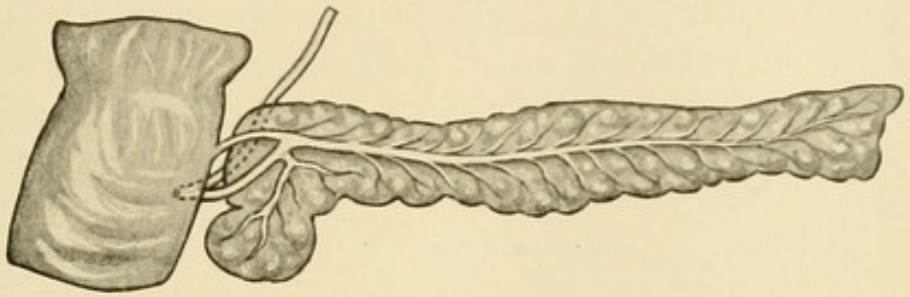

Fig. 7.—Pancreas of the dog, dissected to show the relations of the common bile-duct and pancreatic ducts and their openings into the duodenum.

tomose at two points, and the main duct communicates with the bile-duct before entering the duodenum.

The pancreas of the cat and dog calls for special mention, owing to the frequent use made of these animals in experimental work. The duodenal part of the gland in

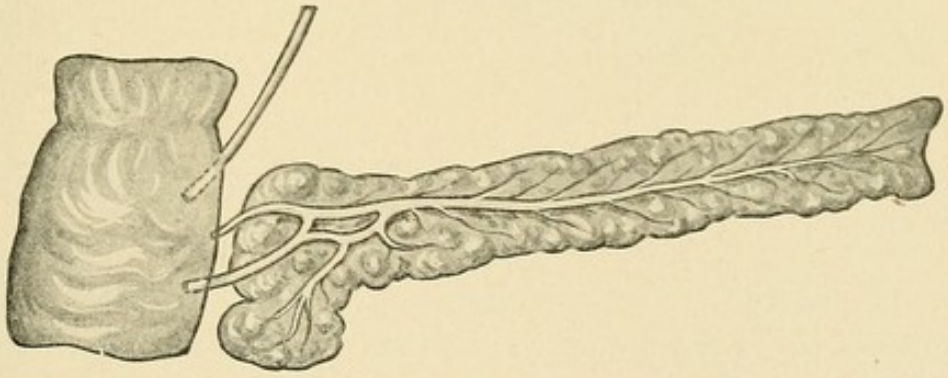

Fig. 8.—Dissection of an abnormal pancreas of a dog, showing separate openings for the common bile-duct and two pancreatic ducts.

the dog is larger than the splenic portion, which it joins at right angles. As a rule, the smaller duct joins with the common bile-duct within the walls of the duodenum, but is externally quite distinct. The larger then enters the

bowel half an inch or more below. Occasionally the bile-duct and two pancreatic ducts have separate openings, as in the case of a dog dissected by one of us. In the cat there is a large duct, communicating with both sections of the gland, which joins with the bile-duct, and enters the duodenum by a common orifice with it. A smaller duct is also present, which anastomoses with the main channel within the gland, but possesses a separate opening into the intestine a short distance below. Occasion-

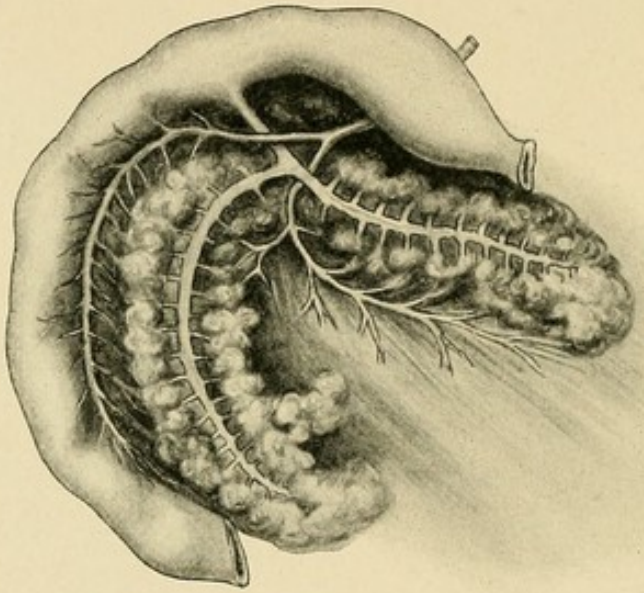

Fig. 9.—Pancreas of the cat, laid open to show the main ducts and their relation to a large vein near the junction of the two ducts (after DeWitt).

ally a lateral reservoir, communicating with the main channel by a short duct just before its junction with the bile-passage, is found.

The pancreas of the anthropoidea is less mobile than in any other group of animals, and is found to be more completely applied and fixed to the posterior abdominal wall, the more adapted the animal is to the upright position. The duodenal part is reduced to an enlargement termed the "head," while the splenic portion narrows at

its termination near the spleen to form "the tail." The intervening portion forms "the body" of the gland, along the thick upper border of which run the splenic artery and vein. The main duct traverses the substance of the gland, nearer its lower than its upper border, and usually communicates, near its termination, with the lesser duct which drains the head. The latter may have a separate entrance into the duodenum, placed somewhat nearer the pylorus than the papilla by which the main pancreatic channel and bile-duct open, or it may be obliterated, the whole of the pancreatic secretion, including that from the head, then finding its way into the intestine by way of the common opening.

Rachford has pointed out that the nearer an animal approaches to the purely carnivorous type, the more likely are the bile and pancreatic juice to be passed into the intestine through a common opening, and the closer is this opening to the pylorus.

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CHAPTER II

ANATOMY

The greater part of the pancreas in man lies in the epigastrium, but a portion of the body and the tail extend into the left hypochondrium, and the head may project into the umbilical region.

To expose the organ from the front the stomach must be detached from the great omentum and be turned upwards. It is then seen as a long, pinkish, cream-coloured gland, stretching transversely across the posterior abdominal wall, from the concavity of the duodenum to the lower and inner border of the spleen. In the fresh condition it has a firm consistency and a markedly lobulated appearance. In length it varies from 5 to 6 inches (12 to 15 cm.). Its average weight ranges from 2.25 to 3.5 ounces (66 to 102 grams). The general shape of the gland is aptly compared by Birmingham, in Cunningham's "Text-Book of Anatomy," to the letter J placed upon its side, ⊣ , the loop being thickened to represent the head, the thickened stem corresponding to the body, and the narrow bend joining the two indicating the neck.

The enlarged right extremity, or "head," extends downwards and to the left, lying in the concavity of the duodenum in contact with its second and third parts, and opposite to the second and, upper part of, the third lumbar vertebra. The short and comparatively narrow portion of the gland termed the "neck" arises from the upper and right part of the head. It runs upwards and to the left, and, after a course of about one inch, merges into the "body." This, which is the longest section of the gland, runs backwards and to the left at the level of

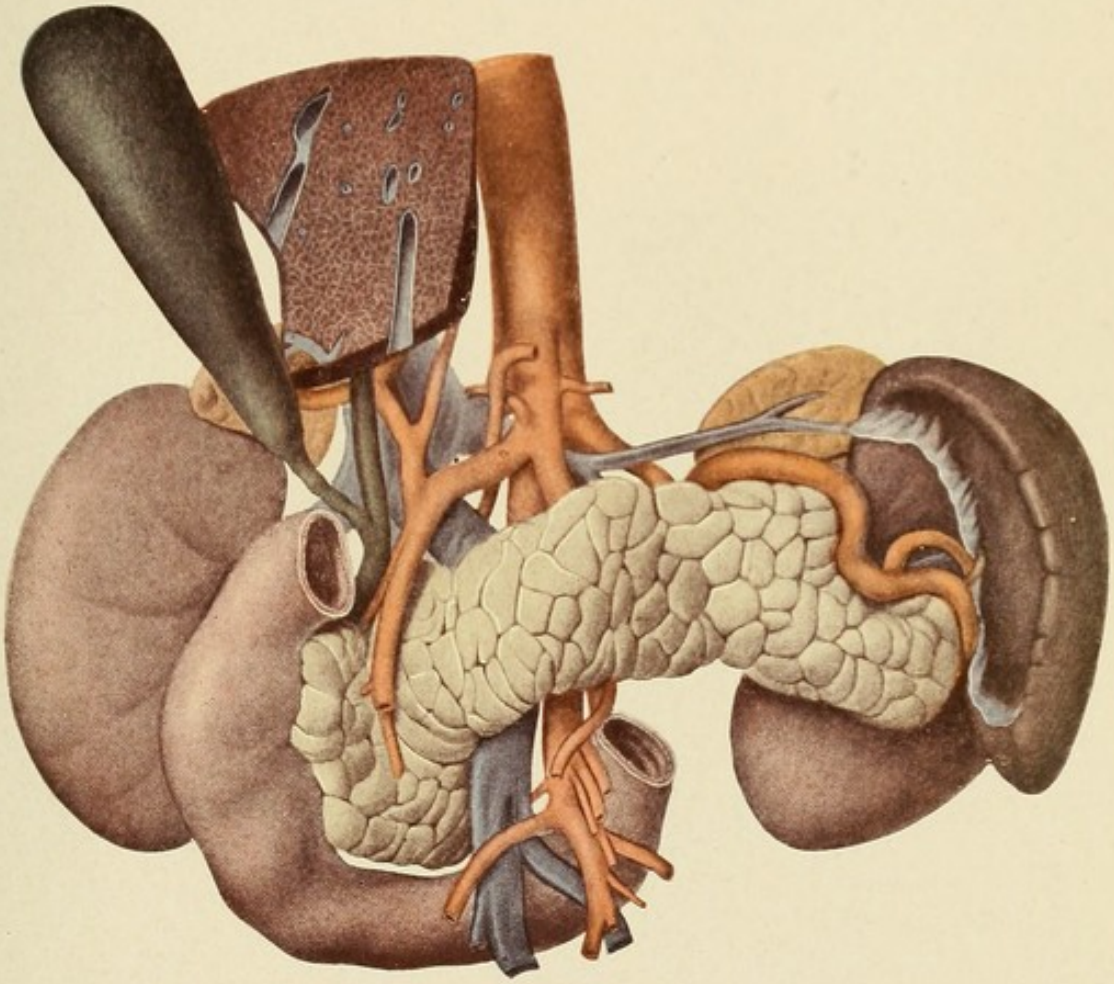

Fig. 10.—Relations of the pancreas (Sobotta and McMurrich).

the first lumbar vertebra. The pointed left extremity, or "tail," is the least firmly attached portion of the organ. It merges so gradually into the body that no sharp line of distinction can be drawn between the two.

The disc-shaped **head** is flattened from before backwards. Its right and lower borders are closely united to the duodenum, one-third of the circumference of which may be enveloped by the gland substance in a well-

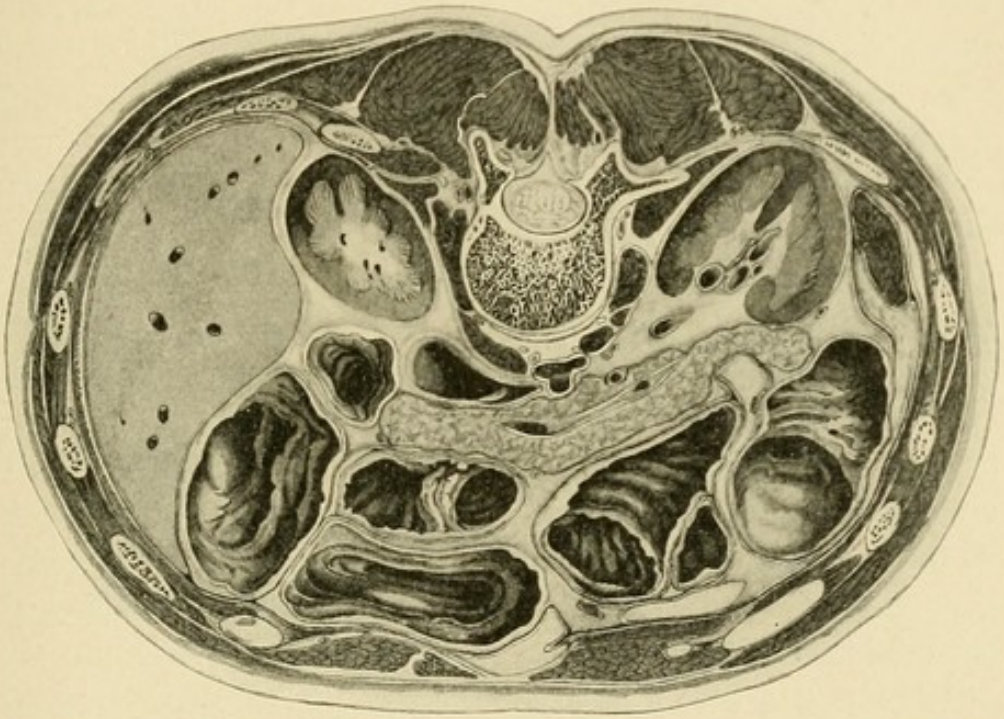

Fig. 11.—Transverse section of the abdomen at the first lumbar vertebra, to show the relations of the pancreas (after Braune).

developed organ. The right half, above, is continued into the neck. To the left, it is separated from the neck by a deep groove, the "incisura pancreatis." In this groove lie the superior mesenteric vessels, which are continued over the anterior surface of the head, near its left border. That portion of the gland which lies to the left of the vessels, along the third part of the duodenum, is termed the "uncinate process," and when, as happens occasionally,

it is separated from the rest, it is known as the "lesser pancreas." The superior and inferior pancreatico-duodenal vessels also course over the head, near its right and left borders respectively, to break up on its anterior surface. Above and to the right, the anterior aspect of the head is in contact with the commencement of the transverse colon, the posterior surface of which is directly attached to the pancreas by areolar tissue. The lower part of the anterior surface of the head of the gland is covered by peritoneum, reflected from the lower surface of the colon and entering into the formation of the greater sac. This part is in contact with portions of the small intestine.

The posterior surface of the head is devoid of peritoneum, and is directly applied to the front of the inferior vena cava, the left renal vein, and the aorta. The common bile-duct also lies in a groove, or canal, in this surface.

The **neck** springs from the upper border of the anterior surface of the head. It passes slightly upwards, forwards, and to the left, to join the body. It is rarely more than an inch (25 mm.) long, is usually about 0.75 inch (18 mm.) wide, and less than 0.5 inch (12.8 mm.) thick. Its junction with the anterior surface of the head is generally grooved by the gastro-duodenal and superior pancreatico-duodenal arteries on the right side. Anteriorly, and to the right, it is in contact with the first part of the duodenum, and also with the pylorus when the stomach is distended. Behind, and to the left, is a groove in which lie the terminations of the superior mesenteric and splenic veins to form the portal vein.

The body and tail together measure about 4 to 5 inches (10 to 14 cm.). They are of a pyramidal shape and present three surfaces of about equal width, averaging 1.25 inches (31 mm.).

The body runs from right to left, and slightly upwards. It is moulded to the adjacent organs, and is thickest in

front of the left kidney. The anterior surface is concave, and looks upwards and forwards. It is separated from

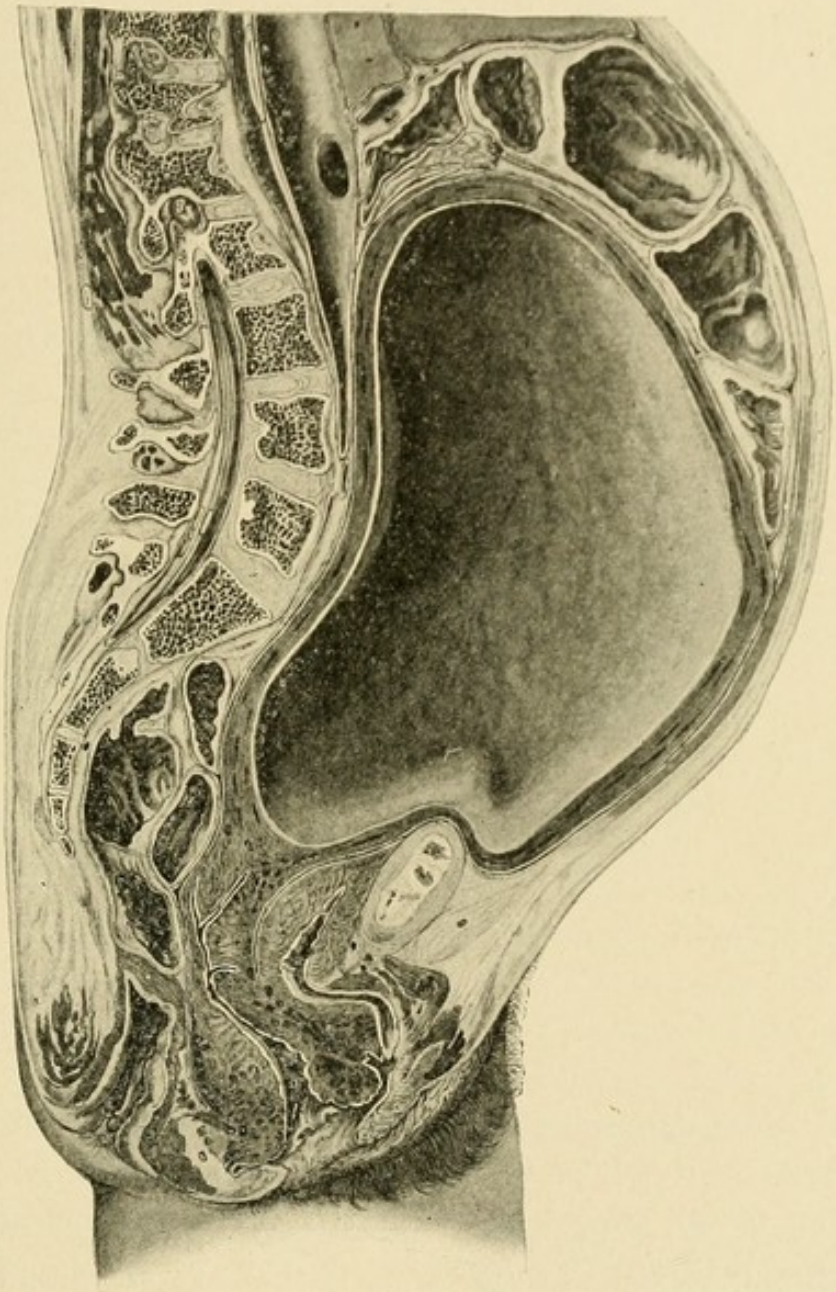

Fig. 12.—Vertical section of the body at full term, showing the relation of the uterus to the pancreas (after Braune).

the stomach by the lesser sac of the peritoneum, the posterior wall of which is intimately attached to it. At

the right extremity of the anterior surface, where the body joins the neck, there is often a well-marked prominence, the "omental tuberosity," so called from its coming into contact with the small omentum when the stomach is distended. The posterior surface looks directly back, and lies upon the aorta, the origin of the superior mesenteric artery, the pillars of the diaphragm, the splenic artery and vein (which run a tortuous course along its upper border in a single channel or may be two separate grooves), the left kidney and renal vessels, and the left suprarenal capsule. This surface, like the posterior aspect of the head, is devoid of a peritoneal covering, and is connected to the abdominal wall and adjacent organs by areolar tissue. The inferior surface looks downward and slightly forward. It is narrowest at the right end, which rests upon the duodeno-jejunal flexure, but widens towards the left extremity, where it comes into contact with the splenic flexure of the colon. At the full term of pregnancy the uterus rises and comes into contact with the lower border. The middle portion is covered by the jejunum. The whole surface is completely invested by peritoneum, derived from the descending layer of the transverse mesocolon.

The tail turns sharply upwards, and backwards. As a rule, it comes into contact with the lower part of the inner surface of the spleen, but occasionally it is separated by a portion of mesentery containing a lymph nodule.

The blood-supply of the body and tail of the pancreas is mainly derived from the splenic artery. The hepatic division of the cœliac axis and the inferior pancreatico-duodenal branch of the superior mesenteric supply chiefly the head. The superior (anterior) pancreatico-duodenal artery is a branch of the gastro-duodenal; passing on to the front of the head, it sends branches into the substance, and also on to the duodenum. The inferior (posterior) pancreatico-duodenal artery arises from the

upper part of the superior mesenteric, or occasionally from the middle colic, artery; it passes upward, and to the right, across the back of the head, and sends branches to it and to the neighbouring duodenum. The two pancreatico-duodenal vessels frequently anastomose around the lower border of the head of the pancreas and form a vascular loop. The inferior pancreatic branch of the

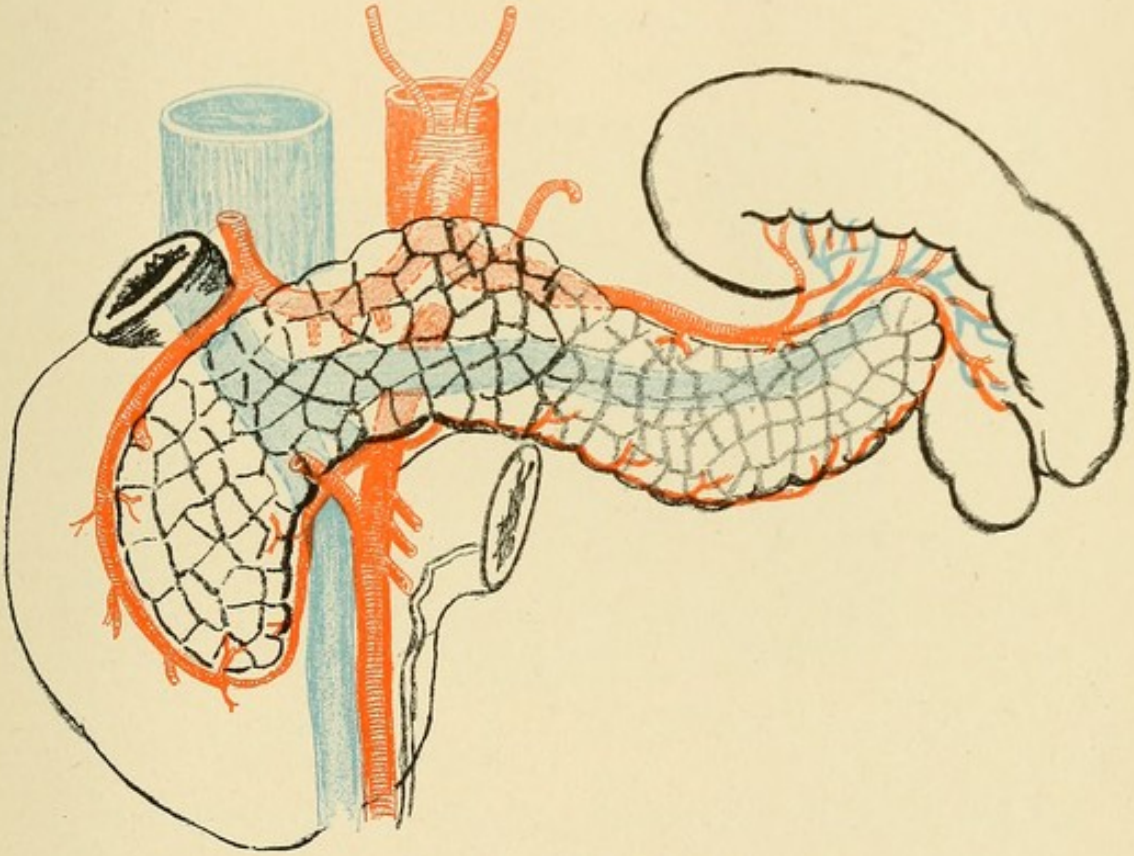

Fig. 13.—Arteries and veins of the pancreas.

superior mesenteric artery runs to the left, along the lower border of the pancreas, often as far as the tail. A large number of small branches are given off by the splenic artery to the body and tail as it courses along the upper border of the gland. Small pancreatic branches are also given off by the hepatic artery as it rests upon the upper border.

The veins are all tributaries of the splenic and superior mesenteric, the blood from the pancreas being thus carried to the portal system. The anterior (superior) pancreatico-duodenal vein lies on the front of the head, and joins the superior mesenteric. The posterior pancreatico-duodenal runs on the back of the head to open into the portal vein. A number of small tributaries of the splenic vein, corresponding to the arterial branches from the

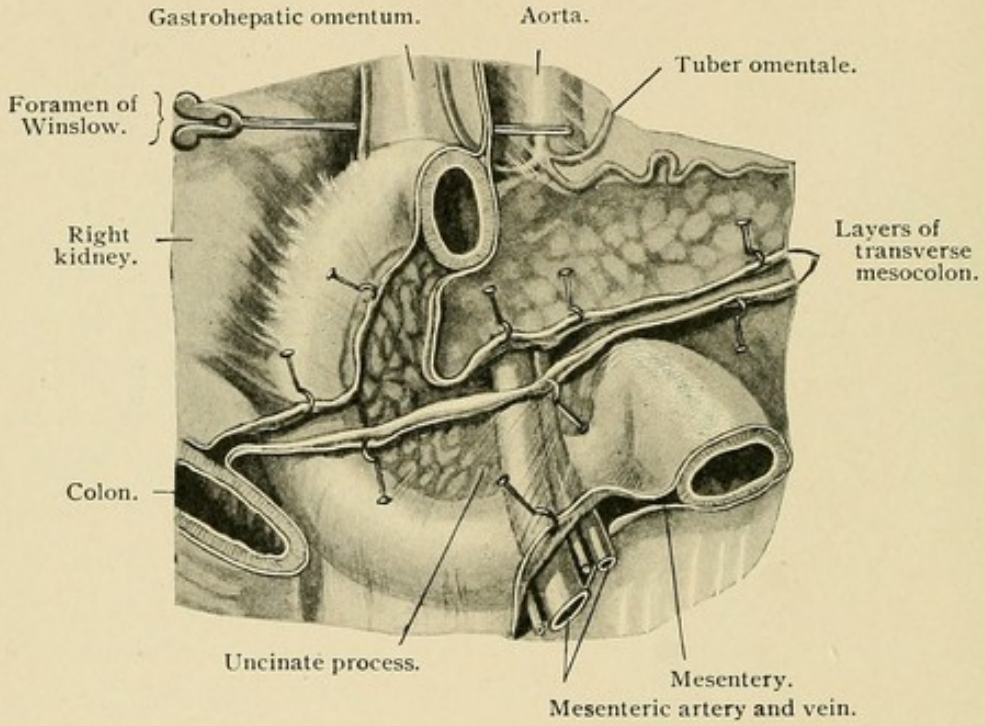

Fig. 14.—Peritoneal reflexions on the pancreas (after Testut).

splenic artery, collect the blood from the body of the gland. There are also many small veins arising in the head and neck which run into the portal vein.

There is a complex network of **lymphatic vessels** in and around the gland, which opens into glands situated on the head of the pancreas, in the hilum of the spleen, and along the superior mesenteric vessels.

The nerves of the pancreas are provided by cerebro-spinal fibres coming from the vagi, and sympathetic

fibres derived from the solar plexus. They accompany the arteries through the cœliac, splenic, and superior mesenteric plexuses, and, travelling in the substance of the gland with the ducts, terminate round the acini in rich plexuses of fibres which send fibres to the secreting cells (Müller). The nerve fibres are almost entirely non-medullated and have minute ganglia on them (visceral sympathetic ganglia cells—R. y Cajal) as they traverse the gland, and near their distribution to the alveoli small cells, apparently of a nervous nature, are also found.

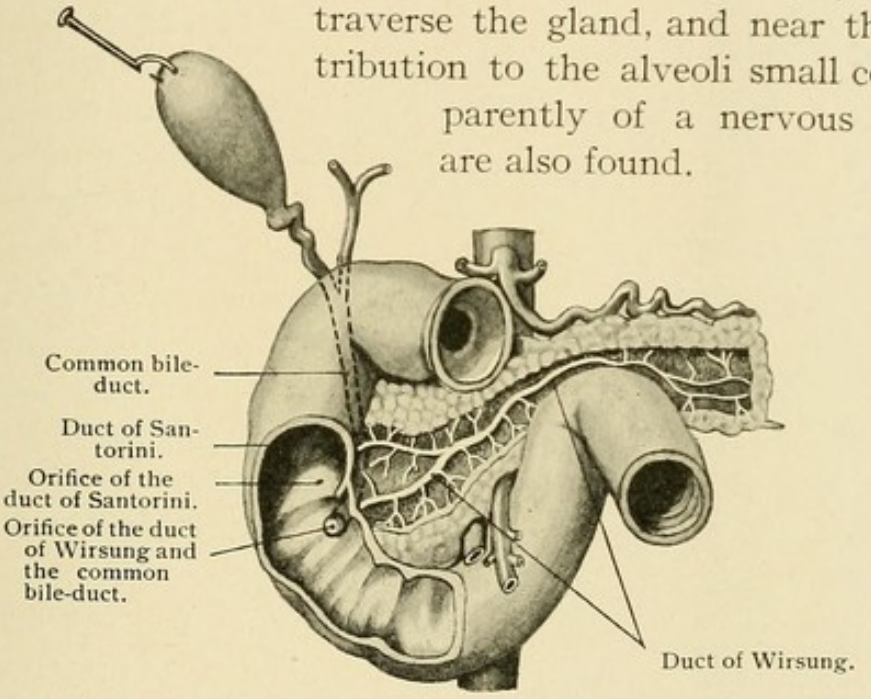

Fig. 15.—The excretory ducts of the pancreas (after Testut).

Peritoneum.—The transverse mesocolon is attached to a line running along the anterior border of the pancreas from the neck to the tail. The anterior layer passes upwards and backwards, over the superior surface, to form the posterior wall of the lesser sac, the posterior going downwards and backwards, along the inferior surface to form the greater sac. At the neck, and on the head, the two sheets of peritoneum have separate lines of attachment, so that a somewhat variable area is devoid of a peritoneal covering and is only separated from the colon by areolar tissue. In many cases, however, the

transverse mesocolon is continued as far as the hepatic flexure, so that the head and neck receive a complete peritoneal investment. The posterior surface is quite uncovered by peritoneum.

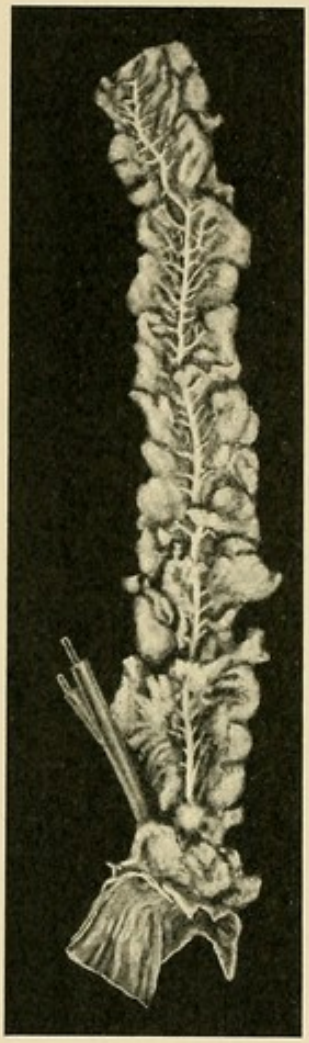

Fig. 16.—Photograph of a specimen in the Hunterian Museum of the Royal College of Surgeons, showing the separate lobules of the pancreas with their ducts opening into the duct of Wirsung (anatomical series 277).

Ducts.—The pancreas has normally two ducts which open separately into the duodenum. The main duct, or *duct of Wirsung*, commences in the tail by the union of the small tributaries draining that region, and gradually increases in size as it courses through the body of the gland from left to right. In the neck it alters its course, bending downwards and backwards, to reach the head of the organ. In the latter it lies nearer the posterior than the anterior surface, and comes into relation with the common bile-duct, beside which it runs to the duodenum. The two ducts pierce the wall of the second part of the duodenum obliquely, about 3 to 4 inches (8 to 12 cm.) below the pylorus, to open into the lumen of the gut by a common orifice, situated on a papilla-like fold of the mucous membrane called the "papilla or caruncula major." Above this there is constantly found a small fold of mucous membrane, which must be raised in order that the caruncle and its orifice may be seen, and running downwards from the caruncle is a small vertical fold known as the "frenum carunculæ" or "plica longitudinalis." Shortly before their

termination the common bile-duct and pancreatic duct usually unite to form a common channel, known as the "ampulla or diverticulum of Vater." This is a small oval or triangular cavity lying in the wall of the duodenum, having its apex at the duodenal orifice, and its base at the openings of the two ducts. Its average length,

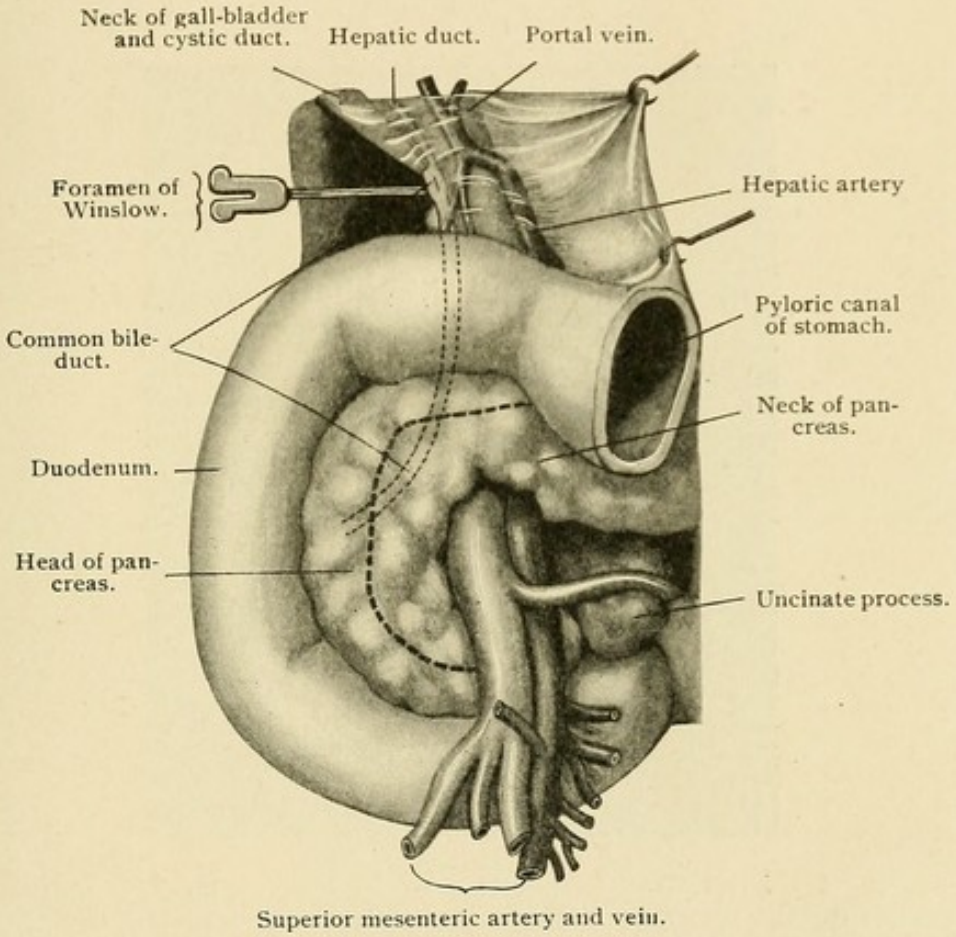

Fig. 17.—Head and neck of the pancreas, viewed from the front (after Testut).

according to Opie, is 3.9 mm. Occasionally it may be as long as 11 mm., while in other cases it is non-existent, the two ducts opening side by side upon the common papilla. The orifice of the common bile-duct into the ampulla is above that of the pancreatic duct, and the two are separated by a small transverse fold of mucous

membrane. The average diameter of the duodenal opening of the ampulla, which is always the narrowest part of the bile channel, is 2.5 mm. (Opie), but in some instances it is equal to, or greater than, the length of the diverticulum. The ampulla, and the terminations of the two ducts, are surrounded by a thin layer of unstriped muscle fibre, forming a sphincter (Oddi).

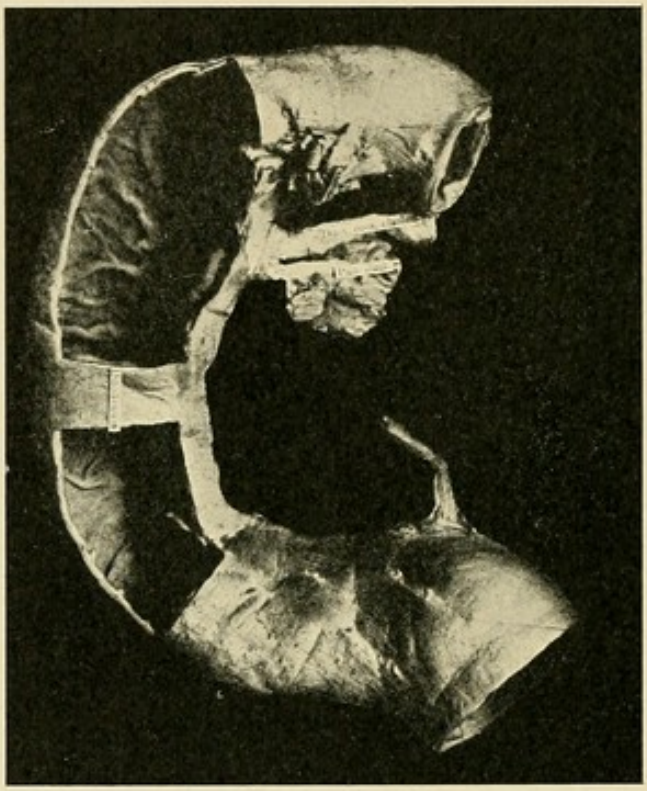

Fig. 18.—Preparation showing the common bile-duct and pancreatic ducts and their common point of entry into the duodenum (Royal College of Surgeons Museum, anat. series 275 B).

The accessory duct, or *duct of Santorini*, is a very variable structure. For a long time it was regarded as inconstant, but more extended and thorough investigation has shown that it is always present, although, at times, it is small, or partly obliterated, especially in the neighbourhood of the intestine. Opie in the examination of 100 bodies found that the duodenal orifice of the lesser

duct was obliterated, or so constricted as to be of little or no functional service, in over half the cases investi-

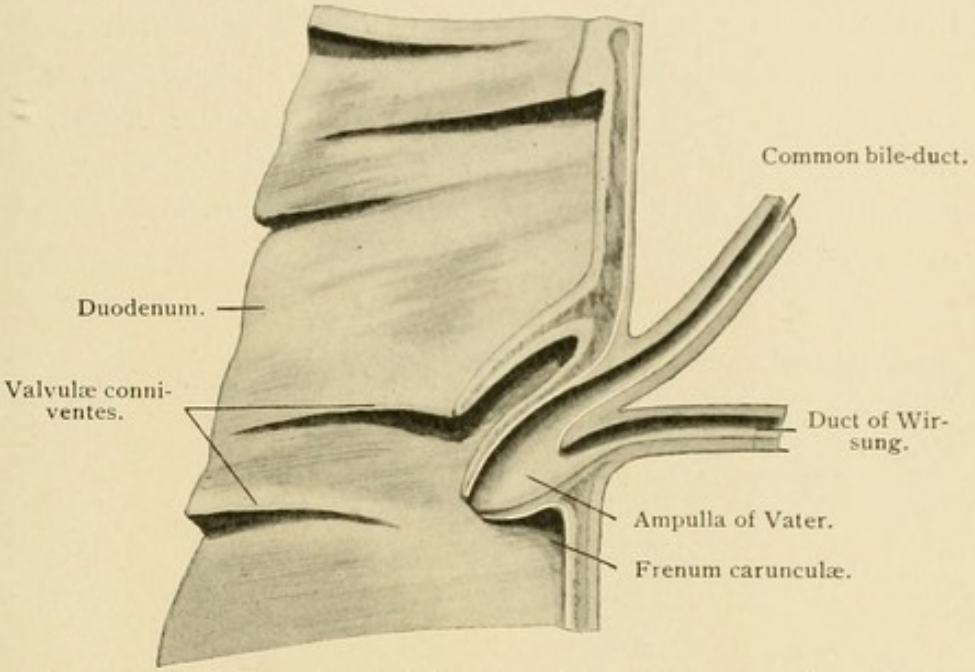

Fig. 19.—Diagram showing the formation of the ampulla of Vater by the union of the common bile-duct and pancreatic duct and their opening into the duodenum (after Testut).

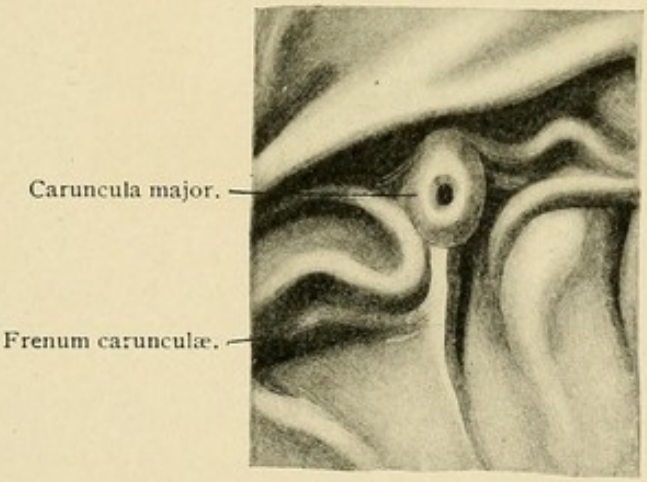

Fig. 20.—Opening of the ampulla of Vater on the caruncula major in the duodenum (after Testut).

gated. The opening, when present, is situated on a small papilla, "the papilla or caruncula minor," lying 0.75 to 1

inch above, and somewhat ventral to, the papilla major on which the ampulla of Vater or the main duct opens. The duct of Santorini is morphologically, and, in some instances, anatomically, the duct of the head of the pancreas, representing what, in the lower vertebrates, is the excretory duct of the duodenal portion of the organ. In man, as in many mammals, the main and accessory ducts communicate with each other within the gland by branches of varying size.

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CHAPTER III

EMBRYOLOGY

It was formerly taught that the pancreas arises in vertebrates by two outgrowths from the walls of the duodenum, the one dorsal and the other ventral, but it has now been shown, for most members of the group, including man, that the ventral bud in its early stages is double, so that

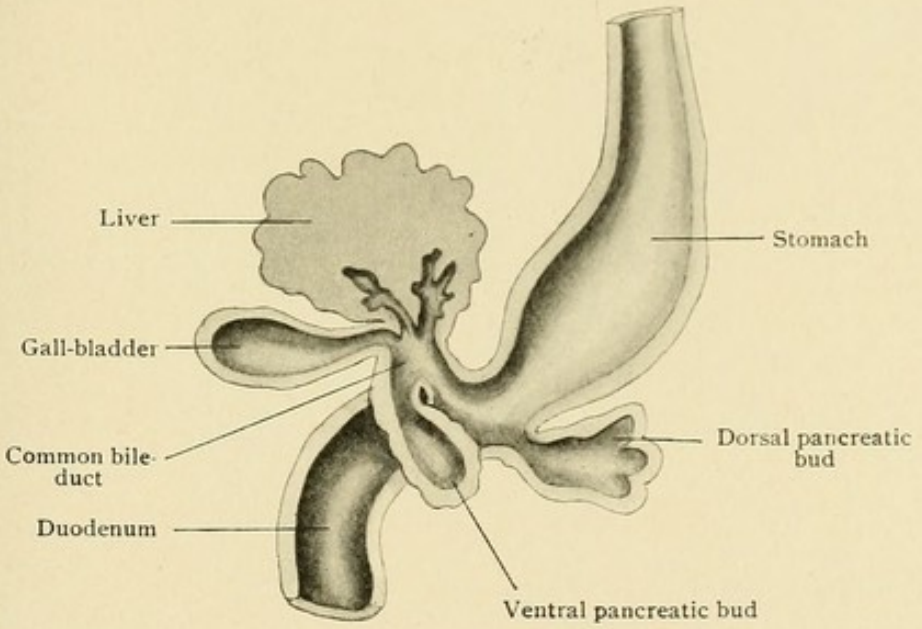

Fig. 21.—The pancreatic and hepatic processes of a fourth-week embryo (after Kollmann).

a triple origin of the primitive rudiment, or anlage, of the pancreas is now generally accepted.

The first indication of the pancreas in man is seen in the fourth week of intrauterine life, as a process from the dorsal wall of what will later become the second part of the duodenum. It grows out between the layers of the dorsal mesogastrium and eventually reaches the spleen,

as it lies above the cardiac end of the stomach. From the opposite wall of the duodenum the two ventral buds take their origin, on either side of the hepatic diverticulum, which has made its appearance at an earlier date. As they increase in size they fuse together to form a single mass, which later unites with the larger dorsal out-

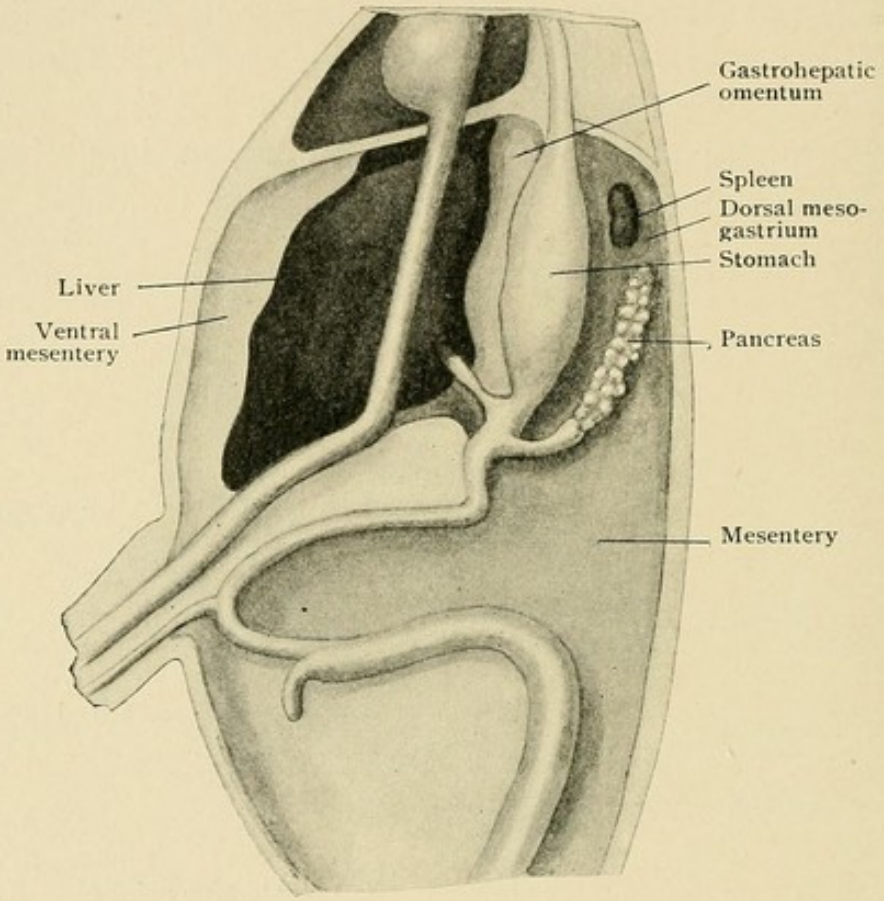

Fig. 22.—The relation of the pancreas, spleen, and liver to the mesogastrium in the embryo (after Keith).

growth. The greater part of the adult pancreas is derived from the dorsal process, the ventral buds only giving rise to the lower part of the head (Fig. 23).

Originally, the gland lies parallel to the dorsal border of the stomach, the head occupying the bend of the duodenal loop and the tail being directed forwards against the spleen. The whole gland is then completely invested

with peritoneum. As the stomach rotates to the left, and the great omentum is developed, the pancreas comes to lie transversely across the abdominal cavity. The former right surface now becomes posterior, and is closely applied to the wall of the abdomen. Its peritoneal covering gradually disappears and is replaced by a connecting layer of areolar tissue. The anterior aspect of the gland, which was formerly its left surface, comes to lie behind

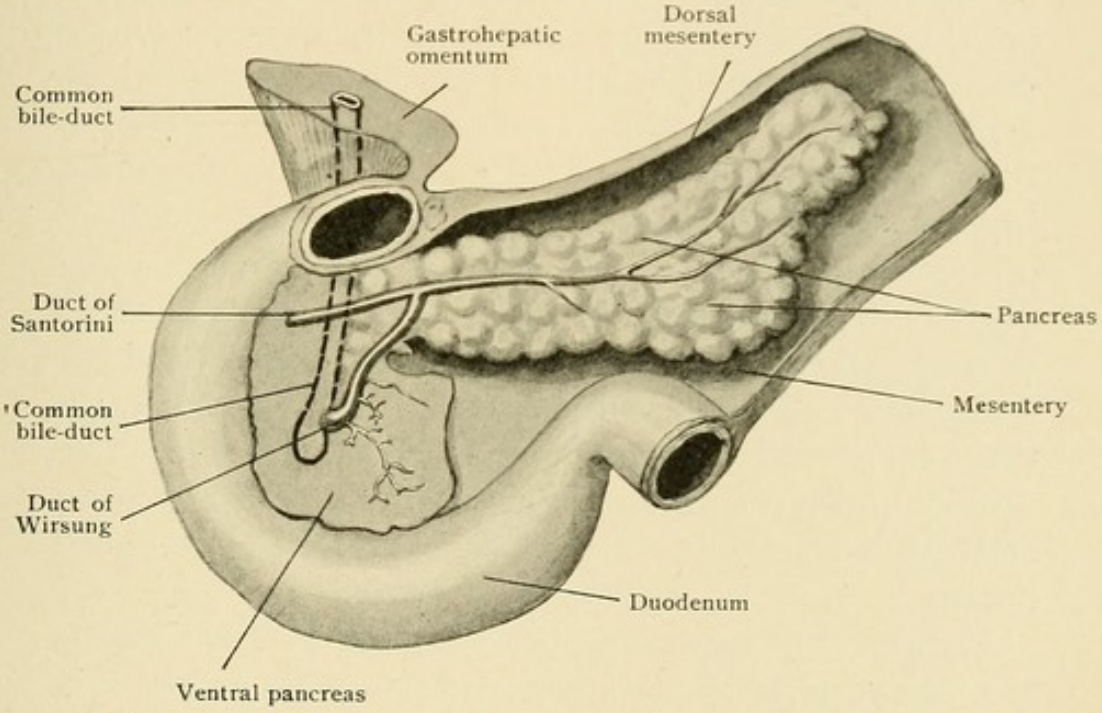

Fig. 23.—Diagram of the pancreas showing its relation to the dorsal and ventral mesenteries, the parts formed from the ventral and dorsal outgrowths; and the formation of the duct of Wirsung by a union between the ducts of the dorsal and ventral buds (after Keith).

the stomach and retains its peritoneal coat, so that the adult arrangement of the pancreas, outside the peritoneal cavity, is reached. In many animals a process from the dorsal outgrowth extends into the gastro-hepatic omentum as an omental lobe, and, in man, this is sometimes found to be represented by a well-marked omental tuberosity.

Each primitive pancreatic outgrowth is provided with a

duct opening into the duodenum. That from the ventral process opens by an orifice common to it and the hepatic diverticulum, close to which it originated. The duct of the dorsal bud communicates with the duodenum by an opening situated nearer to the pylorus. The two ducts almost always anastomose within the substance of the gland at an early stage, and it is found that, as a consequence of this, the chief excretory channels of the adult pancreas are usually of complex origin. The main duct, or duct of Wirsung, of the adult is partly derived from the duct of the dorsal process and partly from that of the ventral outgrowth. That part which lies in the body of the gland represents the main portion of the dorsal embryonic duct, and that which courses through the head, opening into the duodenum along with the common bile-duct, is derived from part of the dilated channel of the ventral pancreatic process. The remaining section of the dorsal duct, lying between the point of anastomosis of the two primitive channels and the duodenal opening, usually undergoes partial atrophy and becomes the accessory pancreatic duct, or duct of Santorini, of the adult organ.

The primary pancreatic processes are hollow, but the secondary, tertiary, and succeeding buds which arise from their walls consist of solid masses of cells. Later these acquire a lumen and the typical structure of the acinotubular pancreas is gradually developed.

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CHAPTER IV

ANATOMICAL ANOMALIES

When considering the anatomical anomalies of the pancreas it is important that the embryology and comparative anatomy of the organ should be borne in mind, for by this means arrangements and distributions of the glandular substance, which would otherwise appear capricious, are explained, and abnormalities of the ducts are simplified.

The abnormality around which most of the literature of the subject centres, and which has aroused the greatest amount of controversy, is the occurrence, in from 0.5 to 1 per cent. of persons, of one or more accessory masses of glandular tissue. These accessory pancreases have been classified by Glinski into three divisions:

1. "*Pancreas minus*," in which a supernumerary lobule, or lobe, is present in the head of the gland, separated by a more or less marked constriction.

2. "*Pancreas accessorium*," where isolated nodules of pancreatic tissue are found embedded in the walls of the gastro-intestinal tract, or in other situations.

3. "*Pancreas divisum*," in which parts of the gland may be found separated from the main mass, but still connected by means of their ducts to the chief excretory channel of the organ.

Pancreas Minus.—Examples of the first variety can hardly be classed as instances of an accessory pancreas, for they only represent, as a rule, an exaggeration of a normal condition, in which a portion of the pancreas is separated from the remainder by a more marked depression than usual.

The commonest is that to which reference has already been made when considering the anatomy of the gland. In this variety a portion of the head, lying behind the mesenteric vessels, is divided from the rest by a deep cleft to form the lesser pancreas ("pancreas parvum" of Winslow). Occasionally, however, the cleft, in which the superior mesenteric vessels lie, is bridged over so that they are contained in a canal in the head of the pancreas, and the descending lobe is thus firmly fixed to the body.

A rarer anomaly, of much surgical interest, is an exaggeration of another normal condition. It has already been pointed out that the head of a well-developed gland may embrace one-third of the circumference of the second part of the duodenum; in rare cases the overlapping is so great that the whole circumference of the bowel is enclosed in a ring of pancreatic tissue. Either at birth, or later if the gland should be invaded by growth or become enlarged from inflammatory changes, it may lead to symptoms of obstruction resembling those due to pyloric stenosis. Shirmer collected four examples of this condition from the older literature, quoting cases by Tiedemann, Becourt, Moyse, and Ecker. More recently instances have been recorded by Symington, Generisch, Tieken, Santos, and Vidal. That of the last named was in a child, and the symptoms, which appeared immediately after birth, suggested congenital stenosis of the pylorus. At operation the true state of things was discovered, and gastro-enterostomy was performed to relieve the obstruction. The patient recovered and steadily gained in weight after the operation. The case operated on by Santos was a woman of twenty-six, who suffered from constant vomiting and was much emaciated. Gastro-enterostomy was performed, but the patient died and the anomaly of the pancreas was confirmed post-mortem (Fig. 24). Symington's case was discovered post-mortem in an adult

male, and is described as follows in the "Journal of Anatomy and Physiology" for 1885: "On distending the intestine with air, in order to facilitate the dissection of the head of the pancreas, it was noticed that the upper part of the descending portion did not become dilated like the rest of the intestine, and on examination this was found to be due to its being completely surrounded in that situation by pancreatic tissue. Two processes of the pancreas passed from the upper part of the head of

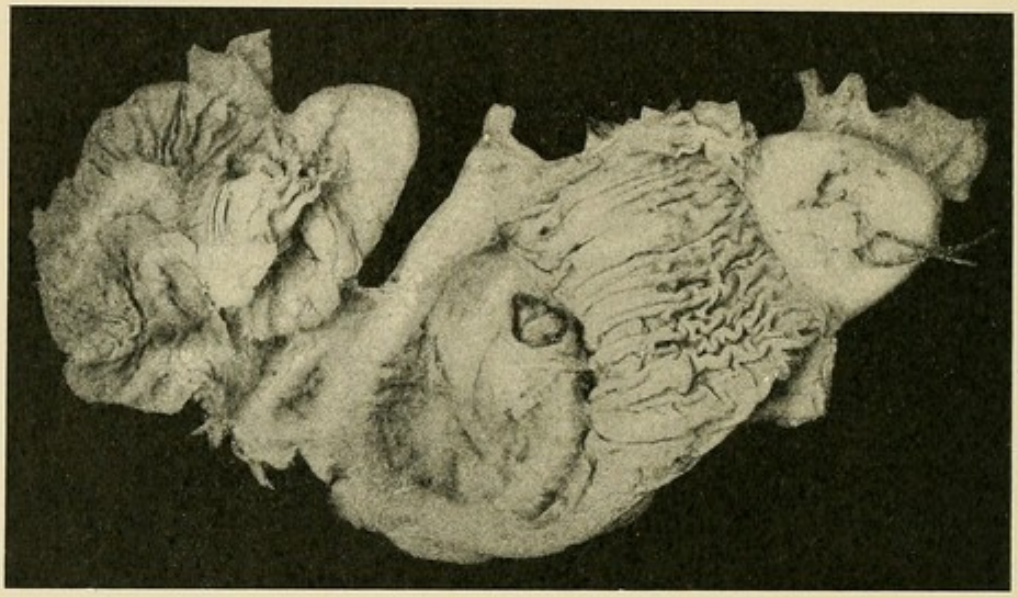

Fig. 24.—Congenital malformation of pancreas compressing the duodenum and leading to obstruction which required gastro-enterostomy. Stomach and duodenum laid open, showing the gastro-enterostomy opening and the stricture caused by the pancreas (Santos).

the gland towards the right, one in front and the other behind the duodenum. They blended on its outer side so as to form, with the head of the gland, a ring of pancreas encircling the duodenum. The processes became somewhat narrower as they passed outwards, and the portion of the gland on the right side of the duodenum was about half an inch in vertical extent. On dissecting out the ducts of the pancreas nothing unusual was observed in their arrangement. The common bile-duct

opened into the duodenum below the seat of the constriction. The circumference of the distended duodenum, where it was surrounded by the pancreas, was two and a half inches, while above and below that it was more than three times as large. In a case operated on by one of us, a prolongation from the head of the pancreas was found extending upwards, in front of the common bile-duct and the hepatic duct, and exerting pressure on both, owing to its being inflamed and swollen.

The body and tail of the pancreas are rarely the seat of anatomical abnormalities. Occasionally the latter is bifid, and a case has been recorded by Klobin in which an enlargement of the tail was found on investigation to contain an accessory spleen.

Glinski's third division, **"pancreas divisum,"** also hardly merits the description of accessory pancreas, for it is really represented by portions of the gland which have become separated by the mechanical pressure of blood-vessels, etc., during development. Hyrtl has described cases belonging to this class in which the head of the gland was separated from the body, a portion of the head lay behind the mesenteric vessels, and the tail was separated from the body of the organ. Engel records an instance in which a portion of the pancreatic tissue was situated under the head, and at the inner side of the descending portion of the duodenum, but was connected with the main pancreatic duct.

Pancreas Accessorium.—The condition to which the term "accessory pancreas" strictly applies, and which most writers describe under that name, is the occurrence in connection with some part of the gastro-intestinal tract of one or more masses of pancreatic tissue in an abnormal situation and independent of the main mass of the gland. It is this which forms the second division of Glinski's classification, the "pancreas accessorium." Accessory masses of pancreatic tissue have been described in the

walls of the stomach, duodenum, jejunum, and ileum. Thorel has maintained that they are most commonly met with in the stomach, but Glinski states that the intestinal wall is the more frequent site. A survey of the literature of the subject tends to support Glinski's contention.

We have been able to meet with records of thirty-seven cases, in which forty-one masses of accessory pancreatic tissue were present, and to these we have to add the hitherto unpublished specimen shown in Fig. 25, from the Leeds Pathological Museum. It was discovered at a post-mortem examination made by W. H. Maxwell Telling and was situated in the wall of the intestine at the duodeno-jejunal junction. In eight instances (Klob, Gegenbaur, Weichselbaum, Glinski, Schirmer, and three by Opie) there was a single nodule in the wall of the stomach. In one, recorded by Opie, there was a mass of pancreatic tissue in the stomach wall, 8 cm. from the pylorus, and a second mass at the pylorus, which on microscopical examination was only found to contain a dilated duct. Opie also describes a case in which an accessory pancreas was found in the stomach, 2 mm. from the pylorus, and another nodule in the wall of the duodenum, 9.5 cm. below the pylorus. Wagner records an instance where an accessory pancreas was present on the anterior wall of the stomach, midway between the pylorus and the cardiac end, and a second nodule, the exact situation of which is not described, in the intestine.

Fig. 25. — Accessory pancreatic nodule in the intestinal wall at the duodeno-jejunal junction.

Twenty-nine accessory masses of pancreatic tissue

have been described in the intestine; all, however, were situated above the ileo-cæcal valve. Six were met with in the walls of the duodenum (Weichselbaum, Zenker, and four by Opie). One of Opie's cases has already been referred to in connection with a similar nodule in the stomach. Four lay in the wall of the duodenum above the pancreas, one was situated on the convex border opposite the head of the gland (Zenker), and one was below the pancreas (Opie). The nodule in Telling's case lay at the duodeno-jejunal junction.

We have been able to find records of nine cases in which a single mass of pancreatic tissue was present in the wall of the jejunum (Klob, Turner, Nicholls, Lewis, Zenker three, and Opie two). In all but one case it lay within two or three feet of the origin of the gut. The exception is described by Opie, and here it was situated 4 metres from the stomach. Zenker quotes a case in which two accessory pancreases were present in the jejunal walls, one 16 cm. below the duodenum, and the second 32 cm. lower down.

The five cases in which an accessory pancreas was found associated with the ileum are peculiar in that the glandular tissue was in each instance situated at the end of a slender or funnel-shaped diverticulum of the intestinal wall(Zenker, Neumann, Nauwerck, Hansemann, Schirmer).

This peculiarity is not, however, confined to the ileum, for in Weichselbaum's case of an accessory pancreas in the stomach wall the nodule was situated at the bottom of a diverticulum near the pylorus, and in cases described by Roth, Opie, and Rolleston diverticula were found on the left side of the duodenum, running into the substance of the pancreas. The fact that the ileal outgrowths have been most commonly found about two feet from the ileo-cæcal valve has naturally suggested that they were the remains of the vitelline duct and examples of Meckel's diverticulum. The occurrence of similar cæcal appen-

dages apart from, and in connection with, pancreatic tissue in other situations along the walls of the gastro-intestinal tract, and the fact that the vitelline duct is already formed when the pancreas begins to develop, are, however, opposed to such a theory. The discovery of a true Meckel's diverticulum, in addition to the intestinal outgrowth containing pancreatic tissue, in three cases has cast further doubt on the suggestion. The shorter forms may be possibly explained by the weakening of the muscular wall of the gut, produced by the inclusion of the pancreatic tissue, which would allow the mucous membrane to bulge outwards under the pressure of the intestinal contents, and to carry before it the pancreatic nodule and remains of the muscular tissue. It is more probable, however, that they are the result of traction exerted during development. The similarity, at least of the pyloric and duodenal diverticula, to the cæca found around the pylorus and along the duodenum of some fishes raises the interesting question as to whether some of them may not be a partial reversion to an ancestral type. A unique case has been recorded by Wright, in which a mass of pancreatic tissue, 3.5 mm. in diameter, was found embedded in the wall of a congenital umbilical fistula, and apparently connected with the persistent remains of the vitelline duct.

Letulle met with five cases in which an accessory pancreas was present in two hundred post-mortems, but unfortunately he gives no details. Opie collected ten examples from eighteen hundred autopsies, which have been included in the foregoing survey of the subject.

The investigations of Helly have shown that in many individuals a small mass of pancreatic tissue, forming a true accessory pancreas, lies in the papilla of Santorini's duct, entirely isolated from the remainder of the gland, and either communicating directly with the duodenum by a separate channel, or draining by a small tributary

into the lesser duct near its termination. Opie has confirmed these observations and described a similar condition in connection with the duct of Wirsung.

The accessory pancreas in all the recorded cases, except those of Klob and Wright, was connected to the adjacent lumen of the alimentary tract, or diverticulum from it, by one or more ducts, which in some instances opened on to a well-defined papilla. In Klob's case it is possible that the duct was overlooked.

The size of the pancreatic nodule varies considerably in different cases. No exact measurements are given in the older records, but a rough idea can be formed from the comparison with a bean and a hempseed, by Weichselbaum, and a pea by Neumann. The largest recorded accessory pancreas is that described by Glinski, which measured 4.5 by 3.5 by 1.0 cm. They are usually much smaller than this, however, and range about 1.0 cm. in diameter. The smallest is described by Opie, and measured only 3 mm.

As a rule, they lie embedded in the muscular tissue of the gut wall, projecting more or less into the submucosa, and beneath the peritoneum, but occasionally they lie in the submucosa only.

Microscopically these accessory nodules have the characters of ordinary pancreatic tissue. Islands of Langerhans were present in cases described by Wright, Opie, and Lewis, but Letulle and Turner were unable to discover them in their cases. In many instances there has been an increase of the interstitial fibrous tissue, indicating that the gland substance has undergone chronic inflammatory changes, and in some the fibrosis has advanced to such a stage that few or none of the glandular elements remained. In such cases the nodule may present characters suggesting an adenoma, or may only consist of fibrous tissue with a few dilated ducts (Opie). It has been suggested that the presence of one or more

masses of accessory pancreatic tissue in the walls of the gastro-intestinal tract may stay, or prevent, the onset of diabetes in cases where the main gland is diseased, but, when the small size of even the largest recorded examples is taken into account, and the frequency with which their contained gland substance shows evidence of disease is considered, it would appear to be unlikely that they can exert any material influence in that direction.

There has been much speculation as to the origin of these accessory pancreatic nodules. Zenker has explained them by supposing that an additional pancreatic rudiment occasionally arises from the duodenum, close to the origin of the normal buds, and that, becoming attached to the stomach, or duodenum, as the case may be, it is carried upwards, or downwards, by the growth of the gastro-intestinal tract, eventually becoming separated from its origin to form a distinct mass of pancreatic tissue in one or other situation. More recently Glinski has suggested that the pancreas of persons in whom accessory pancreatic masses are met with, as well as those of normal individuals, develops from two only of the three buds which are now known to be present in the embryo. Under ordinary circumstances the third outgrowth remains as a rudiment, but occasionally it persists, and, undergoing a limited amount of development, becomes attached to the gastric or intestinal wall as an accessory pancreas. Both these hypotheses only succeed in explaining those cases in which two masses are present by supposing that, in rare instances, a third or fourth pancreatic bud is present in the embryo. Glinski supposes that in such cases the dorsal as well as the ventral outgrowth is double. In disproof of these explanations Opie quotes two cases observed by him. In one there was pancreatic tissue in the walls of the stomach, duodenum, and the lesser papilla, and in the other in the duodenal wall above the pancreas and in the papilla of the duct

of Santorini. He points out that, should an accessory pancreas arise by persistence of one of the two ventral outgrowths, it can only be carried by lengthening of the intestine downwards towards the duodenum, while, should it arise from part of a double dorsal outgrowth, it can only be carried upwards towards the stomach, but that, in these two cases, there were two accessory glands above the pancreas, which can only be explained by the occurrence of a triple primitive dorsal rudiment—a condition which is unknown in the development of any vertebrate animal.

The explanation which he himself offers is similar to that given by Helly for the presence of pancreatic tissue in the papilla of the duct of Santorini. Helly believes that lateral branches from the dorsal embryonic outgrowth may, at an early stage of development, penetrate the wall of the intestine, and later, becoming separated from the rest, acquire new ducts, thus giving rise to the condition found in some cases after birth. Opie, extending this theory, supposes that accessory masses of pancreatic tissue in all parts of the gastro-intestinal tract arise by entanglement of lateral branches of the primitive buds in the developing walls of the alimentary canal, those originating in the dorsal growth being carried upwards to form the gastric and upper duodenal nodules, and those from the ventral bud being carried downwards to constitute the accessory masses of gland substance met with in the lower duodenum, jejunum, and ileum.

Other anatomical anomalies of the pancreas have been described, although they are not numerous. Hertz records a case in which there was falling forwards of the gland; Cacchini describes an instance in which there was congenital displacement of the head of the gland, associated with gastroptosis; and cases have been reported in which the tail of the organ, normally its most movable part, has been dragged into abnormal situations by a

wandering spleen. Klebs states that the pancreas may be pushed downwards by tight lacing, and that retro-peritoneal tumours and aneurysms of the adjacent vessels may carry it upward.

Although the pancreas is one of the most firmly fixed organs in the abdominal cavity it has been occasionally met with in hernial sacs, and Dobrzycki describes a case in which a movable pancreas, giving rise to symptoms resembling those of movable kidney, was present in a man as the result of a fall from a height. The pancreas formed part of the contents of 27 out of 276 cases of diaphragmatic hernia collected by Lacher, and in one case described by Claessen, it had passed through a rent in the diaphragm into the thoracic cavity. Two cases of congenital umbilical hernia in which the pancreas was found in the sac are recorded, and Rose met with a similar relation of the gland in an umbilical hernia in a woman of sixty-four. One case in which the pancreas was apparently entirely wanting has been described.

The **anatomical variations of the pancreatic ducts,** and also of the common bile-duct, have important bearings upon the pathology of the pancreas, and particularly upon the pathology of pancreatitis. It is therefore important that they should be discussed in detail.

The common bile-duct may be divided into four portions:

1. The supraduodenal part.
2. The retroduodenal part.
3. The pancreatic part.
4. The intraparietal part.

Starting by the junction of the cystic and hepatic ducts, it courses along the free border of the lesser omentum, associated with the portal vein and hepatic artery. Then passes behind the first part of the duodenum, and soon comes into relation with the pancreas. Finally it pierces the wall of the second part of the duodenum along with

the duct of Wirsung. The first two portions are unimportant as regards the pancreas, but the relations of the remaining sections have considerable bearing upon the etiology of diseases of that organ.

The third, or pancreatic, portion of the common bile-duct measures from 20 to 25 mm. in length. It extends from the inferior border of the first part of the duodenum to the point where the duct penetrates the wall of the second part. This portion of the common duct crosses a small quadrilateral area, bounded above by the inferior border of the first part of the duodenum, below by the superior border of the third part, externally by the inner border of the second part, and internally by the superior mesenteric vein. Anteriorly it is closely applied to the posterior surface of the head of the pancreas. According to Helly, this portion of the common duct is completely embraced by the head of the gland in 62 per cent. of bodies, and lies in a deep groove in the remaining 38 per cent. Bunger, in a careful examination of fifty-eight subjects, found that in 25 per cent. the duct ran in a groove and in 75 per cent. was entirely enclosed in pancreatic tissue. Wyss investigated the relation of the common duct to the pancreas in twenty-two bodies, and found

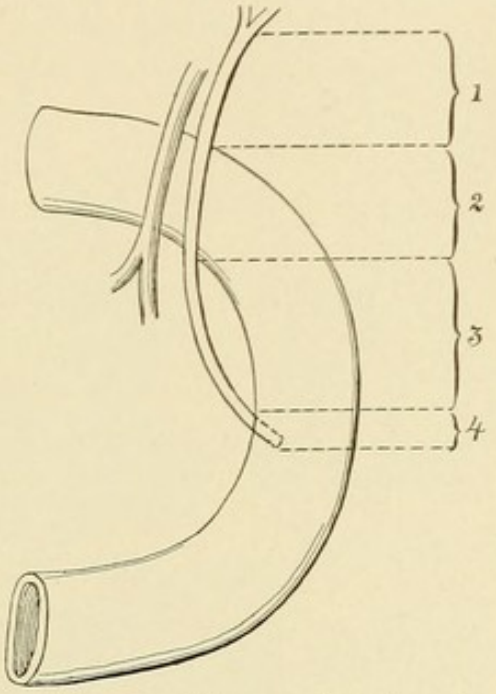

Fig. 26.—Diagram showing relations of the common bile-duct to the duodenum (viewed from behind): 1, Supraduodenal portion of the common bile-duct; 2, retroduodenal portion of the common bile-duct; 3, pancreatic portion of the common bile-duct; 4, intraparietal portion of the common bile-duct (after Testut).

that it was surrounded by the tissue of the gland in seven (31.7 per cent.), and grooved the posterior surface of the head in fifteen (68.1 per cent.). These variations in the relations of the duct to the pancreas are important, for it is obvious that swelling of the gland, when the duct passes through the substance of the head, may compress

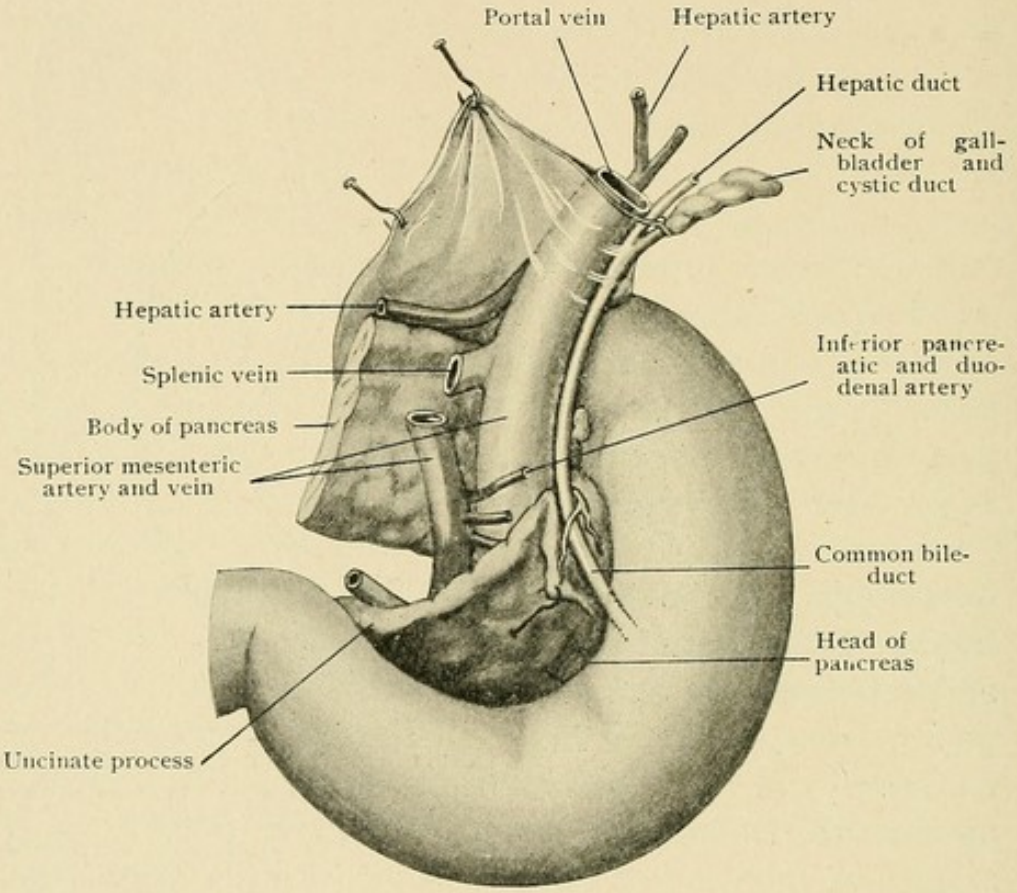

Fig. 27.—Diagram showing the common bile-duct passing through the head of the pancreas, a portion of which has been reflected (viewed from behind) (after Testut).

it and lead to occlusion, while when it is contained in a groove it may be pushed aside and escape compression.

The intraparietal, or interstitial, portion of the common bile-duct comprises that portion of the canal which is contained in the thickness of the wall of the duodenum. Its relation to the duct of Wirsung, and its union with the termination of the chief excretory channel of the

pancreas to form the diverticulum of Vater, have already been described.

The *mode of formation of the ampulla of Vater*, and the terminations of the common bile-duct and pancreatic duct, are liable to great variation, and these variations will be seen to be of considerable importance when we come to consider the diseases of the pancreas. Letulle and Nathan Lorrier distinguish four types:

1. The first, or normal, arrangement, in which the ducts unite to form the ampulla of Vater, has already been dealt with (Figs. 19 and 28, a).

2. In the second type the pancreatic duct joins the

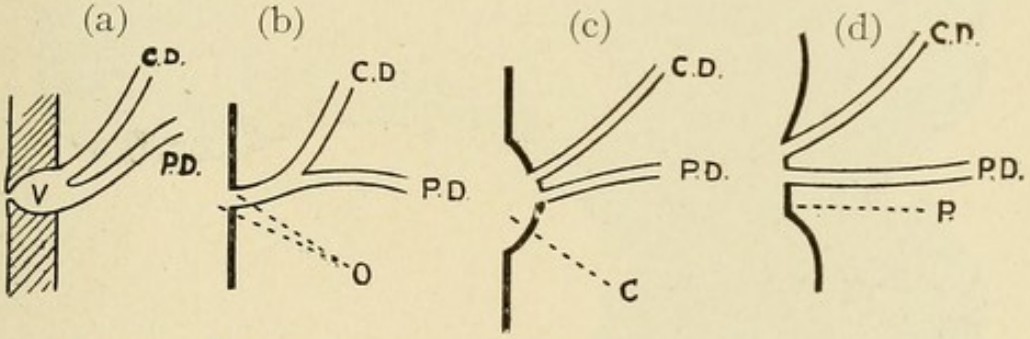

Fig. 28.—Diagram of the four methods by which the common bile-duct and duct of Wirsung enter the duodenum: C. D, Common bile-duct; P. D, pancreatic duct; V, ampulla of Vater; O, common orifice; C, cup-shaped depression in the wall of the duodenum; P, papilla.

common duct some little distance from the duodenum; the ampulla of Vater is absent, and the united ducts open into the duodenum by a small, flat, oval orifice (Fig. 28, b).

3. In the third type the two ducts open into a small fossa in the wall of the duodenum, while the caruncle and ampulla of Vater are both absent (Fig. 28, c).

4. In the fourth type the caruncle is well developed, but the ampulla of Vater is absent, the two ducts opening side by side at the apex of the caruncle. In eleven out of one hundred specimens examined by Opie the arrangement described in this last type was present (Fig. 28, d).

5. Rarely the common bile-duct unites with the duct

of Santorini instead of with the duct of Wirsung, as in a specimen preserved in the Museum of the Royal College of Surgeons (Fig. 29).

The variations met with in the two pancreatic ducts are well shown in a series of one hundred cases investigated with regard to this point by Opie. In every case he found that both ducts were present, although occasionally one or the other was so small that it was demonstrated with difficulty; the duct of Wirsung and the

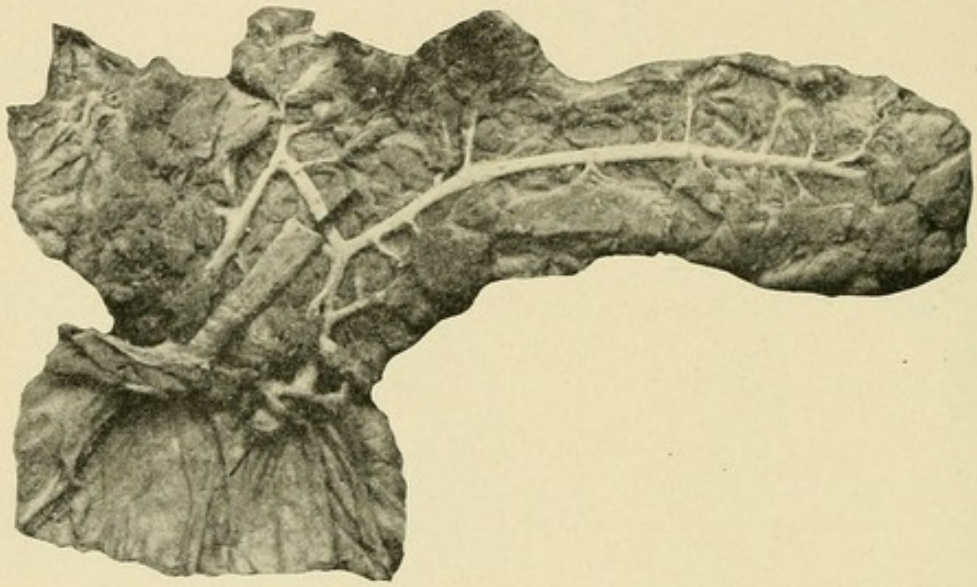

Fig. 29.—Photograph of a specimen in the Hunterian Museum of the Royal College of Surgeons, showing the common bile-duct joining the duct of Santorini (anatomical series 277 A).

common bile-duct always entered the duodenum together, while the duct of Santorini invariably opened into the intestine at a higher level. In ninety specimens the two pancreatic ducts anastomosed within the substance of the gland; in ten there were two wholly independent ducts. On investigating the relative size and the patency of the ducts, he found that out of the ninety cases in which ducts anastomosed the duct of Wirsung was the larger in eighty-four; in these the duct of Santorini was patent in sixty-three, and impervious in twenty-one. The duct of

Santorini was larger than the duct of Wirsung in six, but the latter was patent in all. Of the ten in which no anastomosis between the ducts could be discovered, the

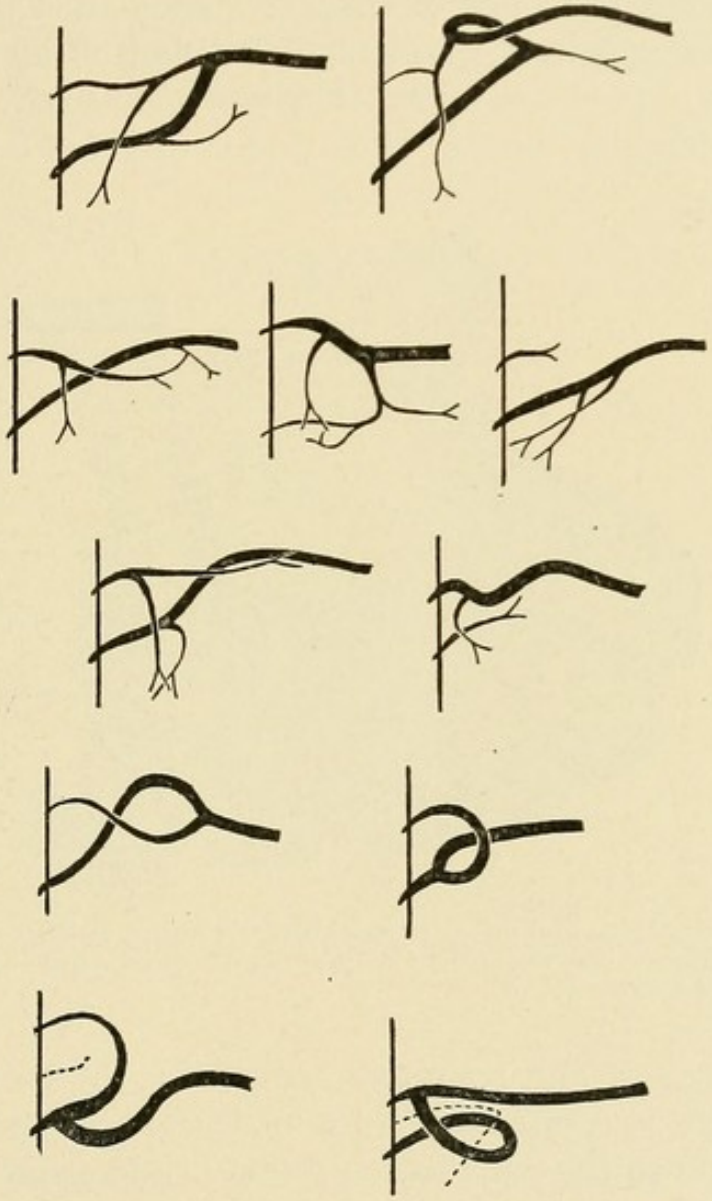

Fig. 30.—Diagram to show the variations in the ducts of Wirsung and Santorini (after Opie).

duct of Wirsung was the larger of the two in five, and the duct of Santorini in the other five. So that in 89 per cent. of the cases the duct of Wirsung was the main excre-

tory channel of the pancreas, and in 21 per cent. the duct of Santorini was apparently obliterated near its termination, and, even in those instances where it was patent, it was found to diminish in size as it approached the duodenum. Thus the duct of Santorini could not be relied upon to supplement the duct of Wirsung in at least 31 per cent. of the cases if the latter was obstructed. Moreover, it must be borne in mind that the duct of Santorini,

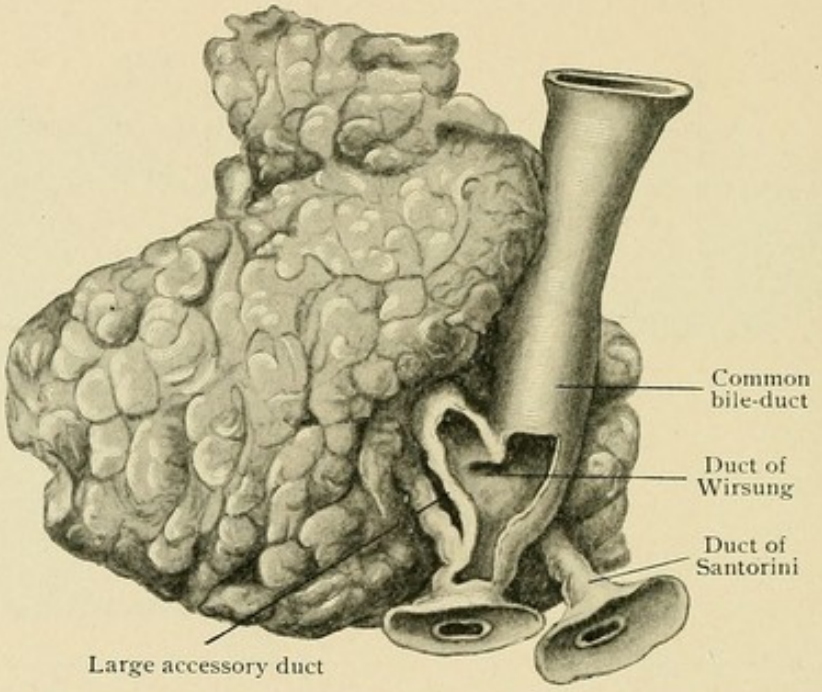

Fig. 31.—Drawing of a preparation showing a large accessory pancreatic duct opening into the ampulla of Vater (Royal College of Surgeons Museum, 277 B).

even if patent and communicating with the duodenum, may itself be compressed by a moderate sized gall-stone passing down the pancreatic portion of the common bile-duct.

In an earlier observation Schirmer obtained somewhat similar results. He examined the pancreas in one hundred and four bodies and found that in sixty-six (63 per cent.) there were two ducts opening into the intestine and communicating with the substance of the gland,

while in thirty-seven cases (35 per cent.) the two ducts did not anastomose, or one or other did not open into the duodenum. In one case three ducts were present. A specimen showing a similar anomaly is preserved in the Museum of the Royal College of Surgeons (Fig. 31). It was discovered during dissection by the prosector to the college, W. U. Pearson.

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CHAPTER V

SURGICAL ANATOMY

The intimate relations of the head of the pancreas to the duodenum may lead to invasion of that part of the

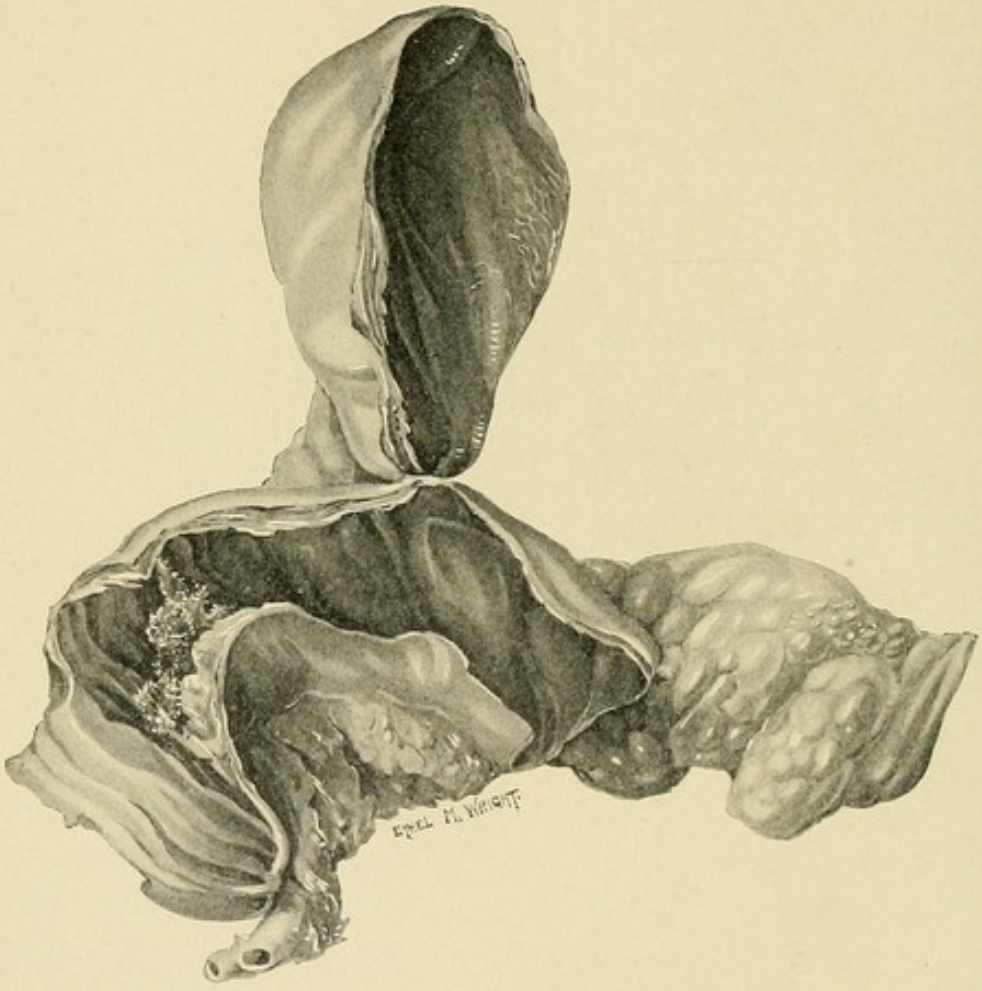


Fig. 32.—Invasion of the duodenum by carcinoma of the head of the pancreas (Leeds Path. Museum, EE 204 A).

intestine by disease of the gland, and, conversely, a primary growth of the duodenum may secondarily involve

the pancreas. Gallaudet has described a case in which a cancer of the head of the pancreas so far obliterated the lumen of the duodenum as to call for gastro-enterostomy, and we have recently had under our observation a case in which a malignant growth of the duodenum gradually invaded the pancreas and eventually gave rise to a severe grade of diabetes. Specimens showing invasion of the duodenum by pancreatic growth are preserved in the Museum at St. George's Hospital (201 A) and in the Leeds Pathological Museum (EE 204 A, EE 204 B). An example of the converse condition is to be seen at St.

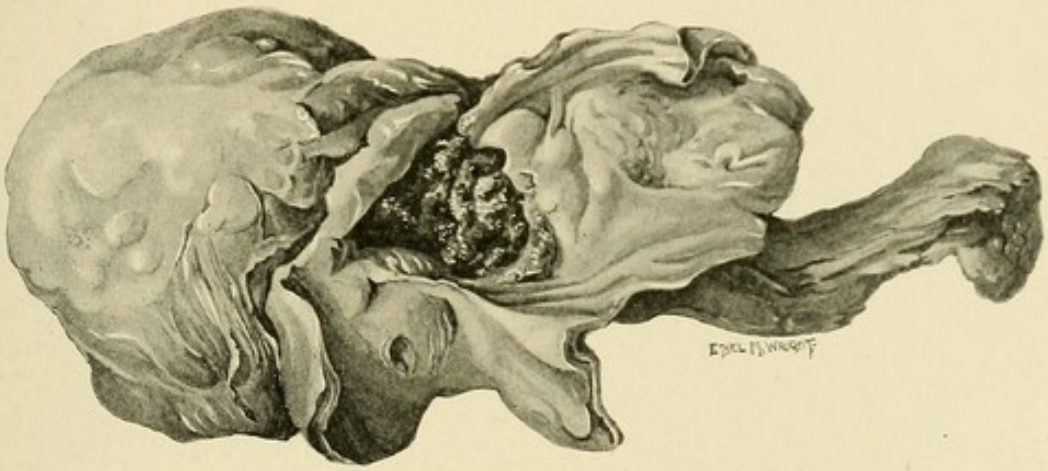


Fig. 33.—Sarcoma of the pancreas invading the duodenum (Leeds Path. Museum, EE 204 B).

Mary's. The duodenum may also be compressed or distorted by cysts or tumours of the pancreas, or may be involved in a pancreatic abscess which may discharge itself into the lumen of the gut.

The proximity of the pancreas to the stomach (Fig. 34) renders it liable to invasion by ulcer or cancer of that organ, and fixation of the stomach by adhesions, whether they arise from disease of the pancreas or of the stomach itself, may lead to a train of symptoms when the latter organ is distended with food, owing to the limitation of its movements in a downward direction, as well as giving rise to

pain, from interference with its normal peristaltic movements. Adhesion to, or invasion of, the pancreas by a cancerous growth of the stomach or pylorus not only adds to the danger of operations undertaken for the relief or cure of the condition, but renders a return of the disease much more probable if removal is attempted. Von Mikulicz's experience on this point is most instructive; in ninety-one partial gastrectomies, without injury to the pancreas, twenty-five died as the result of operation, a mortality of 27.5 per cent.; but in thirty cases in which the pancreas was injured or partly removed the mortality was 70 per cent. (*i. e.*, twenty-one deaths), mostly from peritonitis. Nevertheless, as part of the operation of gastrectomy, a partial pancreatectomy has been successfully performed by one of us, by Mikulicz, by Kocher and others. Fenwick investigated one hundred cases of cancer of the pylorus and found that the pancreas was adherent in six; in another series of one hundred cases of malignant disease of the cardiac end of the stomach the pancreas was adherent in sixteen, and in the same number of cases of cancer of the lesser curvature or posterior wall, it was adherent in nineteen.

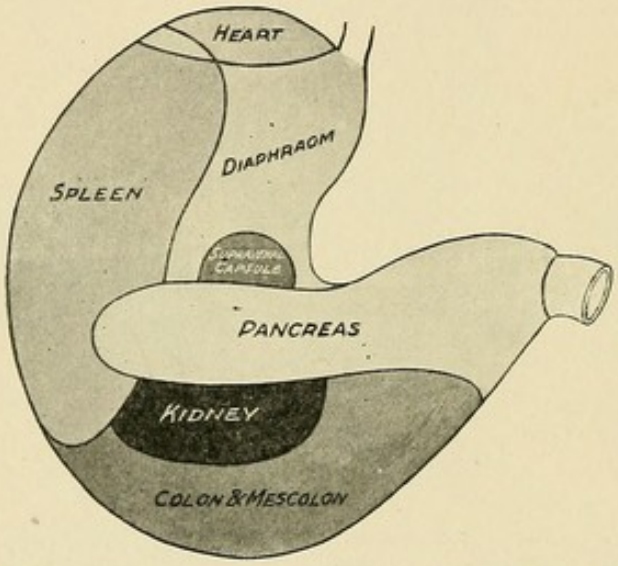


Fig. 34.—Diagram showing the relations of the stomach to the pancreas (after Testut).

Chronic ulcers of the stomach, when they become adherent to the pancreas, may set up pancreatitis, and even give rise to an abscess, as is shown in the case of a man

who was operated upon by one of us six years ago. In this instance the pancreatic abscess had burst into the stomach, giving rise to acute gastritis, with extremely foul stomach contents and incessant vomiting. His symptoms were relieved, and he was eventually cured, by drainage of the stomach into the jejunum through a gastro-enterostomy opening. In another case, also a man, an ulcer of the posterior wall had become adherent

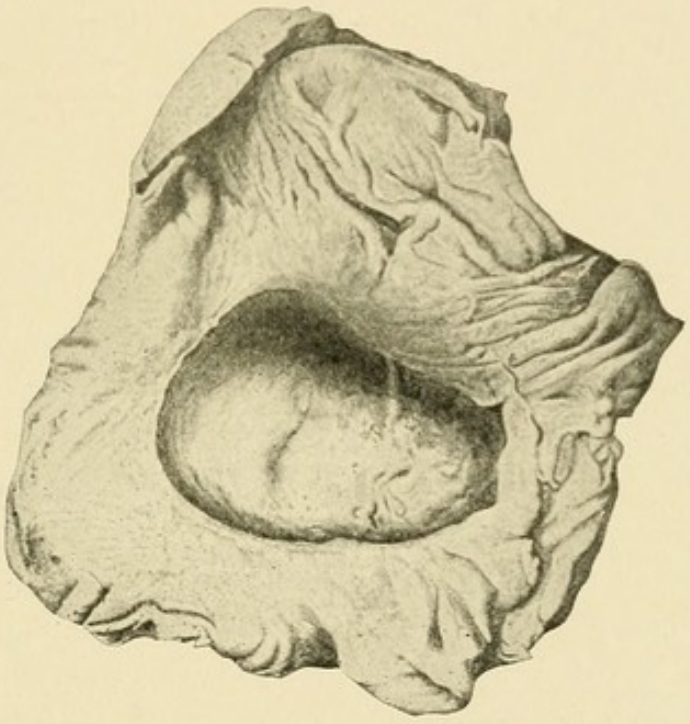


Fig. 35.—Chronic ulcer of the posterior wall of the stomach eroding the pancreas (Fenwick, London Hospital Museum).

to the pancreas and produced a cavity in the substance of the gland into which the tip of the finger could be passed. A third case may be cited in which a middle-aged man had suffered from symptoms of chronic gastric ulcer for several years, with vomiting of coffee-ground material. On exposing the stomach no evidence to account for the trouble could be found, but when it was opened a large ulcer, one and a half by three inches in diameter, was discovered on the posterior wall, eroding

the pancreas. Posterior gastro-enterostomy was followed by complete and permanent recovery.

The relations of the pancreas to the peritoneum are of the utmost importance, both from a surgical and pathological point of view. The retroperitoneal position of the organ is of great importance, for it explains not only the course taken by pus in some cases of suppurative pancreatitis, upwards to the diaphragm and downwards towards the left iliac fossa, but also how such collections may be reached from the right or left loin, especially the latter, by an incision in the costo-spinal angle, or from the left iliac fossa, or between the ribs, when it has travelled upwards and presents as a subdiaphragmatic abscess.

The fact that the anterior surface of the pancreas projects into the lesser sac renders it easy to explain how this cavity is invaded in inflammatory affections or injury of the gland, and, from its shape, it is not difficult to see how, when it is filled with fluid, it is in many instances mistaken for a true pancreatic cyst. The real nature of this variety of pseudo-cyst was demonstrated many years ago by Jordon Lloyd. The sharply limited surfaces of the pancreas, as well as the indefinite site of origin of true cysts of the gland, cause considerable variation in the relations of any tumour which may develop. These relations and the variations induced by the origin of a cyst above or below the transverse mesocolon, and to the right or left of the mesentery, as well as the mistakes in diagnosis which are likely to be caused thereby, will be fully considered in a subsequent chapter (Chapter XVIII).

The situation of the pancreas at the back of the abdominal cavity makes the technique of operations upon it somewhat difficult, unless it is approximated to the abdominal wall by disease, as in the case of pancreatic cysts, or by some special method, such as has been described for exposing the biliary passages.[1] Various routes have

[1] Robson: "Dis. of the Gall-bladder and Bile-ducts."

to be adopted according to the situation of the diseased part and the direction of enlargement of the organ.

The operative methods by which the gland can be exposed may be divided into transperitoneal and retroperitoneal. In the transperitoneal methods it is reached by a median or lateral incision in the anterior abdominal wall, and then either through the gastro-hepatic or through the great omentum, or after pushing up the omentum and transverse colon, through the mesocolon. In each case the omental bursa is opened. Another transperitoneal route, employed by Körte, and by one of us in pancreatic lithotomy and when removing a portion of the gland for microscopical examination in suspected cancer,—by which, however, only the head of the organ can be reached,—is to force a way along the side of the duodenum, the peritoneal covering of which must first be incised. A third method, which is also useful in exposing the pancreatic portion of the common bile-duct, is to incise the parietal peritoneum, lateral to the descending portion of the duodenum, to detach the duodenum from the abdominal wall and then lift it inwards, separating it from the front of the kidney, thus exposing the posterior surface of the head of the gland. The retroperitoneal methods, by incisions in the lumbar regions, only allow of the head or tail of the organ being dealt with, and should therefore be employed only when, through the effects of disease, the affected part is enlarged and pushed to one side or the other, as by abscess, cyst, or tumours.

The anatomical relations of the pancreas to many structures, including the aorta and vena cava, the cœliac plexus, the spleen, the left suprarenal capsule, the left kidney, the portal vein, the duodenum, the stomach and colon, and even the uterus during pregnancy, as well as the common bile-duct and the middle colic artery, injury of which is followed by gangrene of the transverse colon

(Krönlein), have all to be remembered in undertaking operations upon the pancreas.

Its relations to these important structures, its fixation, and its great vascularity would render an operation for the complete extirpation of the pancreas extremely difficult, even if it were justifiable on physiological grounds, but where disease is invading the distal part of the body, or tail, the removal of that portion is both justifiable and safe in the case of cystic or solid, benign or malignant, growths.

The variations in size of the ampulla of Vater have been already referred to, and the bearing of these upon acute pancreatitis will be dealt with when that subject is considered subsequently.

CHAPTER VI

HISTOLOGY

The structure of the pancreas at once recalls that of the salivary glands, hence the names "abdominal salivary gland," "gland salivaire abdominale," "bauchspeichel-druse," that have been applied to it. The resemblance is, however, only a superficial one, for although in its broad lines the pancreas is constructed on the same plan as a serous salivary gland, such as the parotid, its minute anatomy is much more complex, as was first clearly demonstrated by the researches of Langerhans in 1869.

Like the parotid, the pancreas is a compound tubular gland, composed of branching ducts terminating in acini of a tubular form. The acini about the terminal ducts are grouped together to form primary lobules, which in man are usually more or less fused together to form larger secondary lobules about the medium sized ducts. These are again grouped together to form tertiary lobules, which represent the smallest subdivisions of the organ seen on the surface with the naked eye. The larger lobes of the gland are formed in a similar manner by the union of the lobules around the larger ducts. The lobules are less definitely polygonal than in the salivary glands, and they are also less compactly arranged, so that the gland is of a looser and softer texture. The alveoli are much larger and more tubular than in the parotid, and, since they are also relatively more numerous, fewer ducts are seen in a given sectional area.

The arrangement of the connective-tissue framework of the normal pancreas is of importance in view of the changes that occur in it as the result of chronic inflam-

matory affections. Our present knowledge concerning its arrangement and distribution is chiefly due to the researches of J. Marshall Flint, who has made a number of valuable observations on this subject, chiefly by means of the Spalteholz digestion process and with Mallory's stain. The surface of the gland, as we have seen, has no true capsule, but is covered by a loose thin coat of connective tissue. Within the substance of the organ the connective tissue is arranged in an interlobular framework

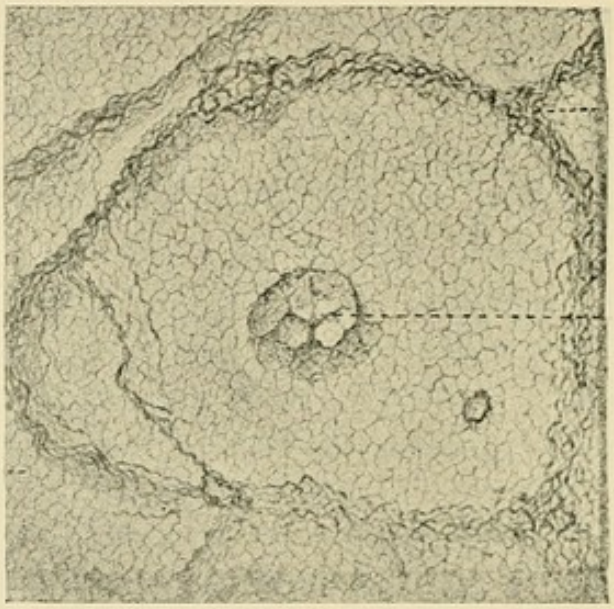


Fig. 36.—Piece digestion of a human pancreas, showing the limiting membrane of a lobule and the reticulated basement membranes of the alveoli. In the center is an island of Langerhans with its capsule of trabeculæ (× 26) (Flint).

of relatively large strands, which separate the lobes and lobules, and an intralobular network of finer fibrils, which lie between the individual acini and so form a plexus within the areas bounded by the coarser interlobular bundles. According to Flint, the interlobular connective tissue is much more delicate and less abundant than in the salivary glands, and is not fasciculated, except in the neighbourhood of the duct of Wirsung, nor are the connective-tissue bundles so regularly arranged. The amount

varies in different parts; in some places only a few strands are found spanning the fissures, while in others relatively thick processes bind adjacent lobules together.

The secondary lobules or lobule groups are usually separated by relatively wide bands of loose connective tissue, but the primary lobules, as pointed out above, are, as a rule, not clearly defined. The intralobular framework is of approximately the same form and size as in the salivary glands, although it is somewhat more delicate, but its arrangement is quite different. It consists of a fine network of delicate interlacing fibres stretching across the lobules between the limiting membranes, and forming a reticulated basement membrane which supports the alveolar cells. The constituent fibres pursue an irregular course and are unequally distributed, being collected in some parts into small bundles, while in others they are seen as narrow strands. Near the islands of Langerhans the processes between the alveoli become thicker and stouter, forming septa which run into the capsule of the island. There is a slight amount of elastic tissue mixed with the fibrous framework, but it is almost exclusively confined to the interlobular regions, excepting around the ducts, which, even in the intralobular septa, are surrounded by a delicate network of elastic fibres. As the ducts unite and become larger the elastic tissue becomes heavier and thicker, but is never laminated as in the submaxillary gland.

The connective tissue lying between the lobes and lobules contains a fair amount of fat. Connective-tissue cells, and occasionally mastzellen, are seen in the interlobular framework, and numerous cells with elongated or polygonal nuclei lie in the interalveolar connective tissue, as a rule on the side away from the lumen of the alveolus.

The lobules do not posses a definite hilus, like those of the submaxillary gland, but receive their blood-vessels

and ducts by separate portals. These structures run, together with the nerves, in the intralobular framework as far as the spaces separating the secondary lobules, but within the secondary lobules themselves the vessels course independently of the ducts and enter the primary lobules at a different point.

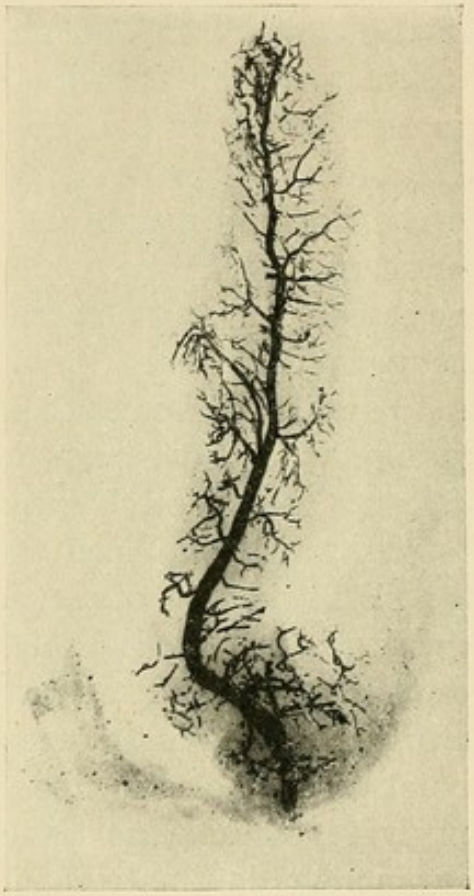


Fig. 37.—Skiagram of a pancreas after injecting the ducts with mercury (Royal Coll. of Surg. Museum).

Both the blood-vessels and ducts are much finer structures than in the salivary glands. In radiographs of the pancreas taken after the ducts have been injected with mercury their extremely fine and delicate character is well demonstrated. By the cruder methods the ducts can probably be injected only as far as their lobular sections, but by forcing in coloured injections under pressure fine intercellular passages between the secreting cells (Saviotti's canals) can be made out. It has been contended that these fine ramifications are artifacts produced by the pressure, but the fact that Golgi's silver chromate method shows similar fine processes between the cells, and even extending into the cell substance (Schäffer), lends support to the results obtained by injection methods.

The walls of the larger ducts consist of an inner thick, and an outer loose, coat of connective and elastic tissue. The epithelial lining is formed by a single layer of colum-

nar cells, which show only faint longitudinal striation. As the ducts diminish in size the connective-tissue coats become less marked and the epithelium assumes a more cubical character, until in the intermediate or intercalary portions it is seen as a single layer of flattened epithelium, the constituent cells of which appear spindle-shaped in

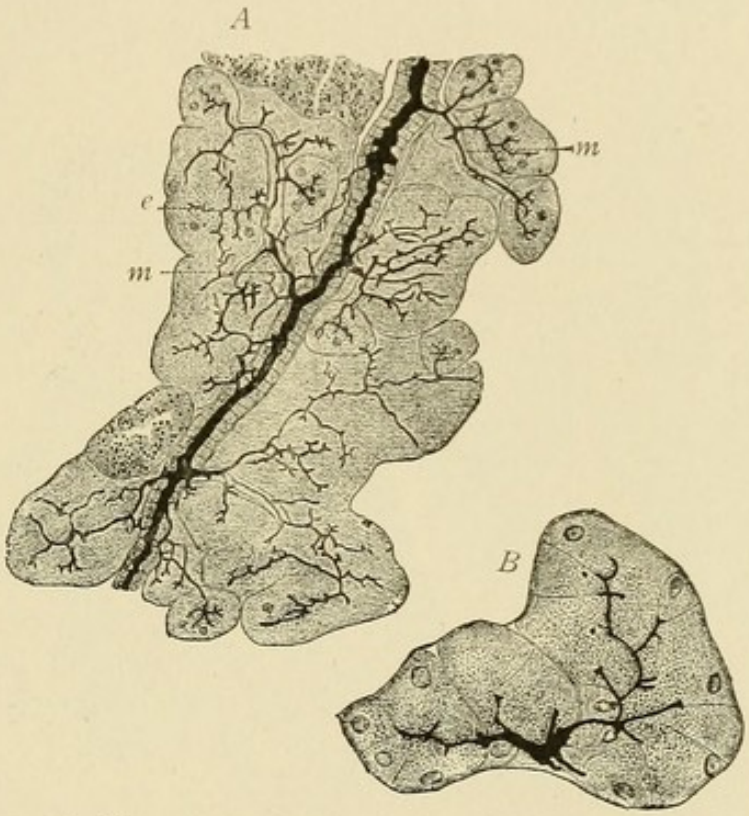


Fig. 38.—Origin of the ducts of the pancreas, as shown by the chromate of silver method (E. Müller): *A*, Duct cut longitudinally, lined by columnar epithelium giving off laterally the intercalary or lobular ductules, *m*, to the alveoli, *e*. The manner in which these commence within the alveoli is shown under a higher power in *B*.

section and do not stain well with either acid or basic dyes. In the largest trunks small mucus-glands can be seen in the walls.

The minute structure of the organ is best studied in the lower animals, for preparations made from the human gland are rarely satisfactory, owing to the rapid changes that take place after death and the interval which usually

elapses before the material can be fixed in a hardening solution. It is also possible to investigate the condition of the gland in animals under various experimental conditions, which, while reproducing more or less closely those obtaining in the human subject in a variety of physiological and pathological states, cannot be secured at will in man himself. Although it is not strictly justifiable to argue from the condition of an organ under any

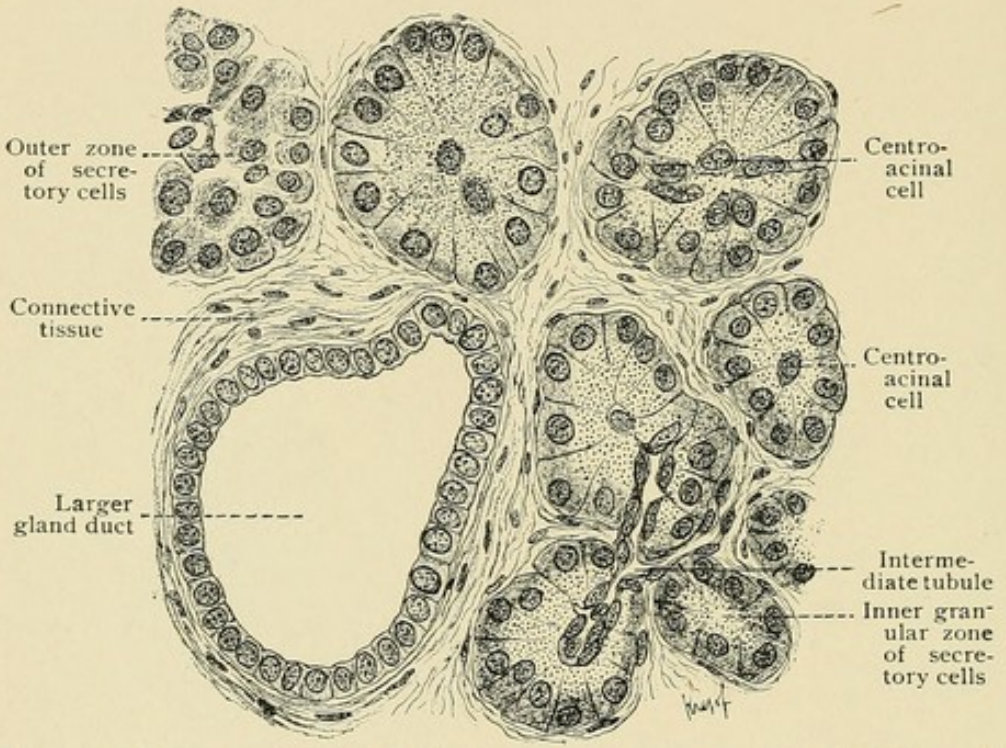


Fig. 39.—From section through human pancreas; ×450 (sublimate) (Böhm and Davidoff).

particular set of circumstances in one animal to what may be expected in its homologue in another under similar conditions, and there are undoubtedly some differences to be observed in the histology of the pancreas in different animals, there is a sufficiently close resemblance in all the higher members of the series to make the advantages of the method outweigh its possible defects.

The alveoli of the pancreas are tubular or flask-shaped,

and are lined by a single layer of columnar cells which taper somewhat towards their central extremities, where they abut upon the small irregular lumen of the acinus.

The nuclei of the cells are centrally placed, as in the serous salivary glands, and there is also generally a spherical para-nucleus. The latter consists of a portion of the protoplasm which stains more deeply than the rest, and is said to be formed by extrusion of material from the nucleus (Gaule, Nocolaider). The protoplasm of the cells contains numerous granules, which stain deeply with acid dyes, such as eosin. The quantity and distribution of these has been found to depend upon the state of the gland as regards its condition of "rest" and "activity."

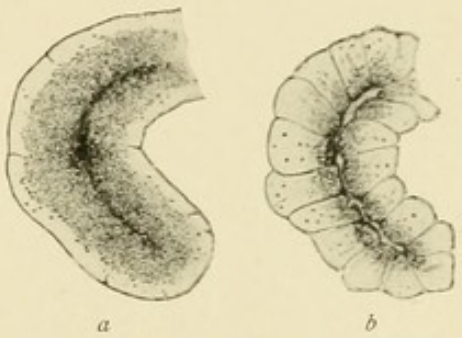


Fig. 40.—Alveoli of rabbit's pancreas during rest (*a*) and during activity (*b*) (Kühne and Lea).

In the "resting," "charged," or "loaded" gland they occupy the inner or central two-thirds of the cells, while in the "active" or "discharged" gland they are comparatively scanty, and are limited to the inner half. According to Heidenhain, during the first stage of digestion (six to ten hours) the granules gradually disappear and the granular inner zone diminishes in size; in the second stage (ten to twenty hours) the inner zone is granular and greatly increased in size, while the outer is small, and during hunger the outer zone again enlarges. All the cells are not, however, in the same stage at the same time, and while in some the granular zone is narrow, in others it may be comparatively broad. The changes observed in the granules during digestion point to their being the zymogen, or precursor of the digestive ferment secreted by the pancreas. Kühne and Sheridan Lea,

watching the effect produced in the lining gland of the rabbit by the injection of pilocarpin, found that secretion of pancreatic juice is accompanied by a diminution in the size of the cells and a discharge of the granules of the inner zone. According to Macallum and Steinhaus, the nuclei possess safranophilous nucleoli, and as the nucleus loses its safranophilous substance the cell substance acquires safranophilous granules. These authors conclude that the chromatin of the nucleus gives rise to a substance, pro-zymogen; sometimes it is dissolved in the nuclear substance, sometimes collected in masses (plasmosomes); finally it diffuses out into the cell protoplasm, and there meets with a constituent of the latter to form zymogen proper.

The protoplasm between the granules only stains faintly with nuclear or basic dyes, but the outer clear zone stains well. The latter is of a homogeneous character, although in some instances it is seen to be faintly striated.

Lying in the lumen of the acini, and sending processes between the secreting epithelium, are small spindle-shaped or branched cells, which, from their position and relation, are known as "centro-acinar cells." They act as supporting elements for the walls of the acini, and, according to Langerhans, are a continuation of the cells of the smaller duct radicles, to which they bear a striking resemblance.

Langerhans, in his description of the pancreas in 1869, first drew attention to those characteristic structures now known as "intertubular cell-clumps," "interacinar islands," or "the islands, or areas, of Langerhans." These are ovoid groups of small spherical or polygonal cells, which, in man, are apparently irregularly scattered through the gland substance, but in some animals, such as the cat, occupy a definite position in the centre of the lobules (Opie). In adult life no connection between the islands and the duct system of the gland can be made out, but

they are found to be intimately related to the blood-vessels.

The structure and relations of the interacinar islands have been the subject of numerous researches on the part of a large number of investigators, who, while agreeing on some points, differ in their descriptions in many important particulars. All those who have devoted attention to the subject agree that very similar structures are found in all vertebrates, but, while some regard them as permanent bodies probably endowed with special functions, others look upon them as being of a temporary nature and consider that they are in reality resting acini.

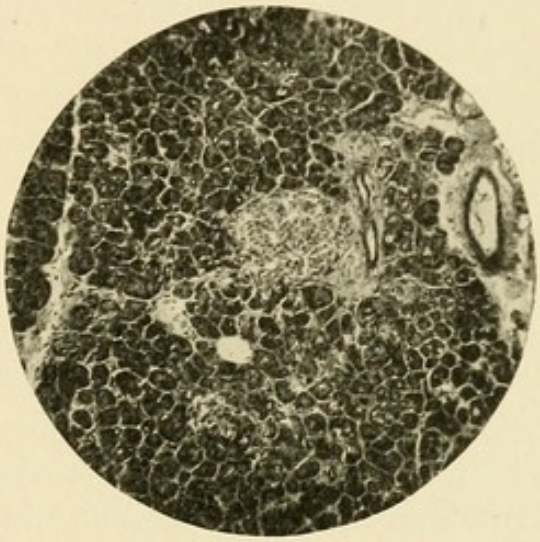


Fig. 41.—Microphotograph of normal human pancreas showing an island of Langerhans and its relation to the blood-vessels (×50).

Harris and Gow in 1894 described three main types in different animals:

1. Those in which the islands were not unlike lymphoid tissue, consisting of many deeply stained nuclei with little or no distinct cell protoplasm (*e. g.*, the guinea-pig).

2. Masses of non-granular cells with distinct outlines, which were joined in an irregular network (*e. g.*, armadillo).

3. Compound cell-groups in which the islands were divided by strands of connective tissue into smaller groups (*e. g.*, human).

In 1899, however, Von Ebner stated that all these types could be found in one and the same animal, and suggested that the different appearances depended upon

the amount of blood in the capillaries. Subsequent investigation has shown that the cells are of a similar type in all mammals and that the classification adopted by Harris and Gow does not hold good.

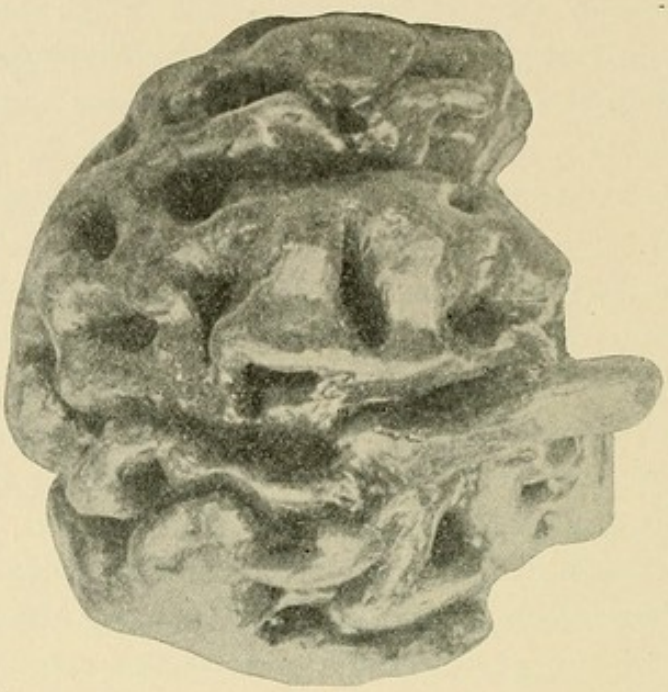
The cells are always smaller than the gland cells, and each possesses a centrally placed round or oval nucleus. The nuclei differ from those in the secreting cells by being usually larger, relative to the amount of cell protoplasm, and having a very fine chromatin network with small nucleoli. The protoplasm of the well-defined cell bodies is very finely granular, containing numerous very small fat droplets. It does not stain at all with basic nuclear dyes, such as hæmatoxylin, but has some affinity for eosin and other acid stains. The appearance of the cells differs somewhat in some members of the vertebrate series; thus, in birds the cells are generally small, oblong in shape, and stain very poorly; in the frog the preponderant cells are tall and columnar, and are arranged in single rows between the blood-vessels, so that each cell is in contact with blood capillaries on two sides. This arrangement of the cells in rows between the blood-vessels, so characteristically seen in the amphibia, is found in the mammalia to some extent, although in them several rows of cells usually intervene between two adjacent capillaries.

All observers are agreed that the islands of Langerhans are richly vascularised, but there is some divergence of opinion as to the nature of the vessels. The most recent observations are those of Pensa (1905) and Lydia M. De Witt (1906). Pensa states that, as the result of injections of the blood-vessels in a large number of different animals, he was able to show that the islands are mostly supplied by a rich capillary network which is continuous with the intertubular capillary plexus. In some animals, such as birds, guinea-pigs, and dogs, the larger islets may have, in addition, a small afferent artery breaking up into a capillary plexus and then collecting again into a

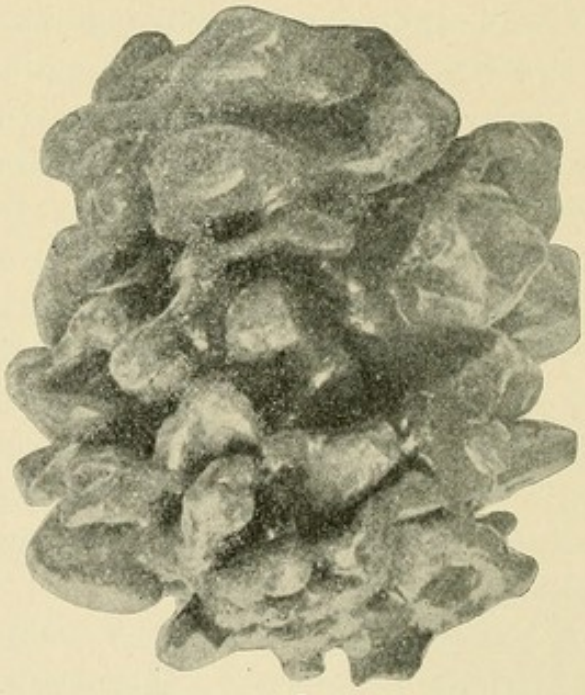
single efferent vein. As Lydia De Witt points out, however, he does not explain how he distinguishes the arteries from the veins, and while he states that the connection is, as a rule, purely capillary, one of his figures seems to indicate that the connection with larger vessels is common.

By reconstructing the islands by the Born wax-plate method, and by a study of serial sections from injected and uninjected preparations, Lydia De Witt has made most valuable contributions to our knowledge of their morphology and histology. She comes to the conclusion that in all the animals she has investigated, including man at different ages, cats, rabbits, rats, birds, guinea-pigs, and frogs, the cords of cells forming the areas are separated by large irregular anastomosing vessels, having a complete endothelial wall, but little or no adventitia, thus corresponding to Minot's definition of "sinusoids." The endothelium of the sinusoids is directly applied to the epithelium of the islands, intervening connective tissue when present, as in the human adult pancreas, being secondary. The vascular network, according to her observations, is derived from the branching, winding, and anastomosing of several large venous channels and many capillaries which communicate intimately with the interacinar capillaries. The largest sinusoids are situated at the centre of the islands, where the cells are smallest. The periphery of the areas is much less vascular. Von Ebner also considers that the large blood-vessels of the islands are venous, and he points out that they are surrounded on all sides by cells like the blood capillaries of the liver lobules.

By means of preparations made by Golgi's method Pensa showed that the islands of Langerhans are supplied with a very rich network of nerve fibres, which pass along the blood-vessels and between the cells. The number



A



B

Fig. 42.—*A*, Wax reconstruction of areas of Langerhans from human pancreas (× about 245); *B*, wax reconstruction of blood-vessels with surrounding connective tissue in same area (× about 245) (De Witt).

and arrangement of the fibres were found to be quite different from those met with in the acini.

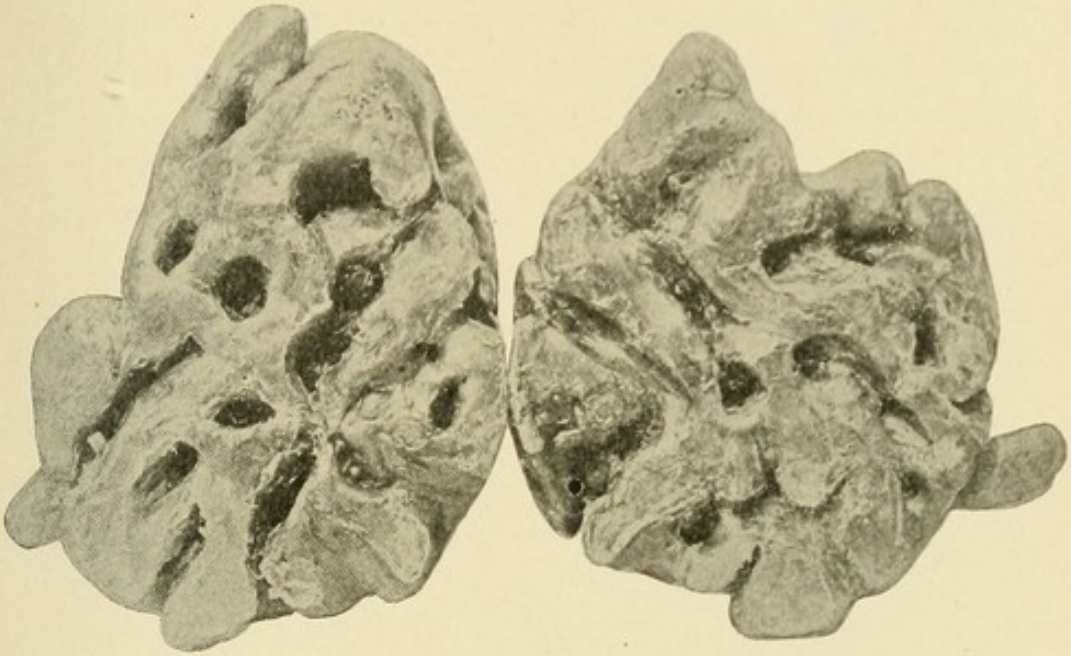


Fig. 1.

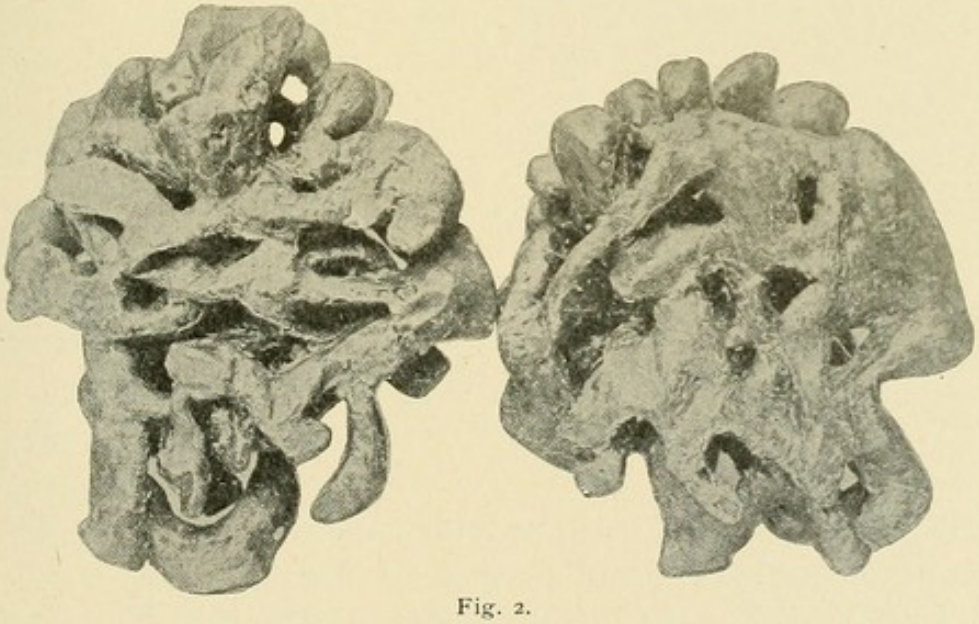


Fig. 2.

Fig. 43.—1, Interior of the model shown in *A* in the preceding figure; 2, interior of the model shown in *B* in the preceding figure (DeWitt).

The relation of the cell islets to the excretory ducts of the pancreas has been investigated by Von Ebner, Kühne

and Lea, Lewaschew, and Dogiel. The last named made use of Golgi's method, while the others forced injection masses into the ducts. They all, excepting Lewaschew, came to the conclusion that, in the adult, the cell islets are not connected by permeable ducts with the excretory system of the gland, but Lewaschew found that some of the injection material passed within the islands. His results, however, are generally regarded as having been due to accidental escape of the injection mass. Lydia De Witt, in her paper, states that the reconstruction method and her study of serial sections shows "that the cords of cells have the external form of branching and anastomosing tubules, with occasional alveolus-like enlargements; they are, however, solid structures with no lumen and no arrangement of the cells and nuclei which would suggest a lumen."

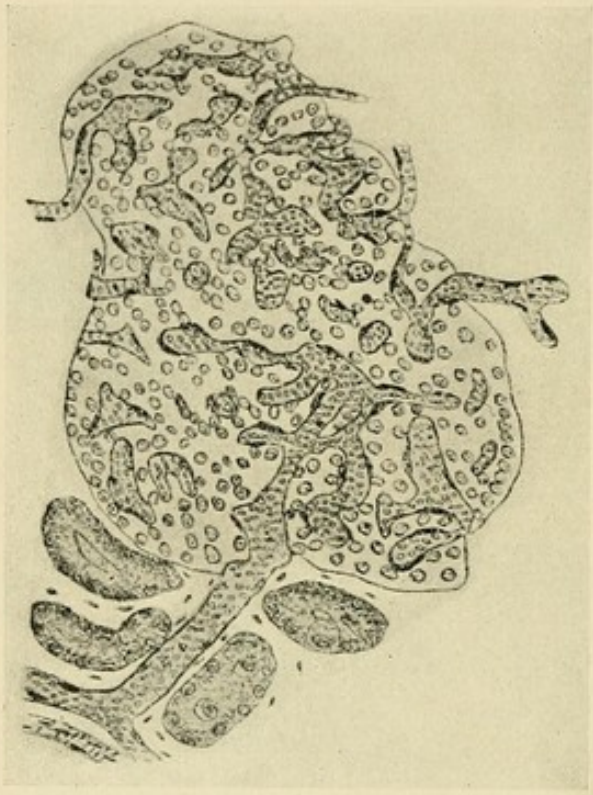


Fig. 44.—Section of an island of Langerhans from the pancreas of a rat in which the veins were filled with blood, showing the connection with the large vein and the arrangement of the sinusoids within the island (× 200) (DeWitt).

In speaking of the intralobular framework of the gland it was mentioned that Flint's investigations, by means of the Spalteholz digestion process, showed that near the islands of Langerhans the processes between the alveoli become thicker and stouter, forming septa which run

into the capsule of the island. According to Flint, this capsule is a well-defined structure, and the connective tissue forming the framework of the islands has a characteristic arrangement in sharp contrast to that of the remainder of the lobule. He found that the capsule is composed of thousands of ultimate fibrils, which, on the one side, are connected with the alveolar network, and, on the other, with the septa or trabeculæ which stretch across the space within the island, subdividing it into smaller lacunæ and acting as a support for the cells of which it is composed. Every island in the gland has the same characteristic appearance and general conformity in the arrangement of its framework, and no transition stages can be found between the two.

Laguesse, however, was unable to find a fibrous tissue capsule, but describes a thin, homogeneous layer, thickened in places, which forms a "pseudo-capsule." He also states that a thin amorphous sheath accompanies the principal vessels, and may be continued over the capillaries. Von Ebner was also unable, as a rule, to find any connective tissue, or membrana propria, between the capillaries and cells of the islets.

These apparently contradictory statements are to some extent explained by the observations of Lydia De Witt. This observer found that in the frog no connective tissue can be demonstrated, either surrounding the areas or around the intra-insular sinusoids, but that in the guinea-pig, rat, and rabbit, sections stained with Mallory's stain show a very thin connective-tissue capsule separating the island from the surrounding pancreatic acini, and delicate sheaths of connective tissue covering the blood-vessels, while delicate fibres also follow the contour of the cells. In the human subject the age and condition of the body appear to be most important factors in determining the amount and distribution of the intra-insular connective tissue. The pancreas of the new-born infant,

according to her, shows most of the islands to be situated in the inter-lobular connective tissue, by which they are surrounded, but no connective tissue could be made out within the cell islets themselves. In a four-year-old child, although no connective tissue could be demonstrated with ordinary stains, Mallory's stain revealed a delicate capsule and delicate sheaths surrounding the blood-vessels. Around most of the cell-islands of the adult a rather definite capsule of nucleated connective tissue was found, and in the interior definite trabeculæ, divid-

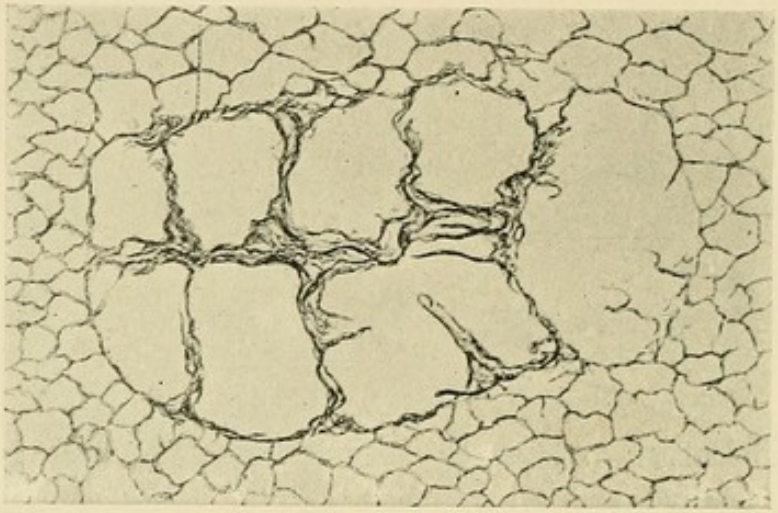


Fig. 45.—Piece digestion of a human pancreas, showing the connective tissue of an island of Langerhans from Fig. 36 (× 135) (Flint).

ing the islands into smaller compartments containing the cells, could be seen. In some instances the connective tissue formed, with the larger blood-vessels, one or many large trabeculæ passing through the centre of the area, and from them smaller branches were given off to the sides, much in the same way as that described and figured by Flint (Fig. 45).

The very small amount of connective tissue found in the islands of Langerhans in animals and young persons, and the increase which apparently accompanies advancing age in man, as a rule, suggest that it is probably a

secondary effect analogous to the fibrosis which is usually associated with advancing years in other organs.

The size and distribution of the islands is not uniform. Laguesse has distinguished five different types in man, varying from a very small form, less than 100 μ in diameter, to very rare, giant forms of over 400 μ in diameter. He found, from an average of six bodies, that there is rather less than one island to each square millimetre of pancreatic tissue, and that about 0.01 per cent. of the gland is formed by the islands of Langerhans.

Opie found that they were more numerous in the tail, or splenic end, than elsewhere in the human pancreas. He also agrees with Kasahara that the pancreatic tissue of the fœtus and very young children shows a larger number of islands than that of the adult. He states that this can be explained if it is assumed that they are formed during embryological development, and persist unchanged while the secreting tissue increases in bulk. Lydia De Witt, however, found that while about 0.02 per cent. of the pancreas of the adult consisted of insular tissue, it formed 0.04 per cent. of that of the four-year-old child and only 0.008 per cent. of the pancreas in the new-born infant, and that the average size of the islets in the adult was actually greater than in either of the other two.

The position of the islands with regard to the rest of the pancreatic tissue is not constant in the human subject, although they are often situated in the centre of a more or less clearly defined lobule, but in the cat they occupy a position near the centre of the lobule, each of which, in the splenic portion, contains an island (Opie). Their distribution in certain bony fishes, particularly in Lophius piscatorius and Scorpœna scropha, is of considerable interest and importance, as bearing upon the questions of their origin and significance. Rennie states that very large islets were found in the areas of pancreatic tissue scattered along the abdominal vessels in all of the

twenty-five species he investigated, and that in Lophius piscatorius and Scorpœna scropha there was constantly present a very large, so-called "principal islet," independent of the pancreatic tissue, and surrounded by a fibrous tissue capsule, in the mesenteric fold between the portal vein and mesenteric artery, a short distance in front of the spleen. These principal islets are sufficiently large to be distinguished by the naked eye and can be dissected out free from pancreatic tissue. In the pancreas of the guinea-pig Lydia De Witt met with large, relatively isolated islets lying in the connective tissue around the large ducts, especially about the junction of the splenic and middle thirds, and, occasionally, in the mesenteric fat near the periphery of the gland, cell islets, which appeared to be free from the pancreatic tissue, were met with. The majority of the islets were, however, closely related to the pancreatic acini. The same observer noticed that in all the sections from the new-born infant examined by her the islets were situated in, and were surrounded by, the interlobular connective tissue.

Light on the vexed question of the significance of these remarkable structures has been sought by a study of their development, but here again there is considerable difference of opinion. Hansemann believed that they arose from the interstitial tissue and had no connection with the pancreatic acini. Laguesse, studying sheep embryos, described a double origin for the islands. The so-called "primary islands" are said by him to arise from deeply staining units in the single layer of cells forming the wall of the primitive pancreatic tubules. By their proliferation these particular cells form solid outgrowths, which, later, becoming surrounded by the hollow outgrowths which bud out from the primitive tubules, constitute the primary cell islets. The secondary islands were believed by Laguesse, following Lewaschew, to be transitory structures developed from the acini and

changing back into them again. Küster states that they are derived from the ducts; Pearce believes that they are developed from the pancreatic tubules, and are at first solid and later become vascularised, a reticulum developing still later. Renaut states that the primitive dorsal and ventral duodenal outgrowths form solid branches which ramify in the mesentery. These later acquire a lumen, and from their walls groups of blind pouches arise, which constitute the secreting acini, each group of pouches representing a primary lobule of developed pancreas. In each group of pouches there appears a cell, similar to those described by Laguesse, and by the continued growth and multiplication of this the cell islet of the lobule is formed.

The constant presence of these structures at all ages and in so many different animals, their early appearance in embryonic life, the manner in which they retain their vitality under varying conditions, their different staining reactions, and peculiar arrangement, have suggested that they are independent vascular glands, derived from the same embryonic rudiments as the secretory acini, but endowed with some special function. Although this is the view held by most recent writers who have devoted attention to the subject, there are others, as we have already mentioned, who regard them as temporarily changed acini which may again assume their former appearance and characters. The principal arguments advanced in favour of the latter hypothesis by its supporters are: (1) that the islets are closely related to the acini, from which they are not separated by any definite capsule, both structures have a common blood-supply, and the islets open into the pancreatic ducts; (2) in the same sections various transition stages between typical acini and typical islets can be found; (3) the number of islets increases during activity of the gland and diminishes during rest; (4) by prolonged stimulation of the

gland, either by overfeeding or by the administration of pilocarpin, it is possible to transform secreting acini into islands of Langerhans; (5) if the pancreas of a guinea-pig is ligatured near the splenic end in two places, and portions are examined at intervals from between, behind, and in front of the ligatures, while all traces of gland substance disappear from the tissue between and behind the points of constriction, the cirrhosed portion in front shows as many, if not more, islands of Langerhans than secreting acini, so that, although the results seen in the last named may tend to support the theory that the islands are independent and more resistant structures than the acini, the same cannot be said for the remaining parts (Mankowski). The points raised under the first heading have been discussed in considering the structure of the islands, and it has been shown that the most recent observations do not lend support to these contentions. There is no doubt that in some of the lower animals, such as the rabbit, in which the capsule of the islands is very thin, places can be seen in which the island cells and the gland cells appear to be continuous, and that in the fœtal pancreas affected with congenital syphilis the islands of Langerhans may be continuous with the surrounding secreting structures (Opie). But this can be explained, in the one case by

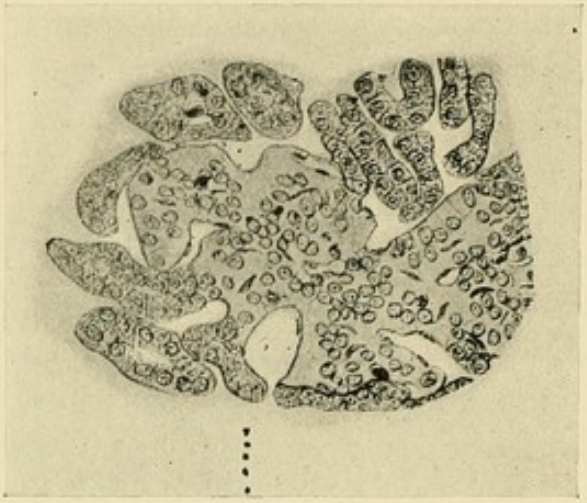


Fig. 46.—Section through the center of an island of Langerhans from the pancreas of a rabbit, showing a connection with the pancreatic tubules at "*p*" (× 200) (DeWitt).

the more or less rudimentary condition of the organ, and in the other by the retarding effects of the pathological condition on development, for, as we have shown, it is probable that the secreting cells and the islets originate from a common epithelial anlage. With regard to the second point, it cannot be disputed that at times structures suggesting transitional forms are met with, but by the study of serial sections it can generally be made out that these are either gland acini in which the staining reactions are abnormal and the characteristic differentiation into zones is absent, or cell islets in which the eosinophile cells are more numerous than usual. Lydia De Witt states that in her experience she has seen none that could not be explained in some other and more rational way than by supposing that they were transition forms between secreting acini and cell islets, and that the so-called transition forms have proved to be merely resting pancreatic tubules. The same observer has examined, measured, and counted large numbers of islands from a considerable number of guinea-pigs to determine the changes brought about by digestion and diet. The animals were killed about fourteen hours after eating and were kept upon (1) normal full diet, (2) without food or drink, (3) on pure carbohydrate diet, (4) on pure meat diet. She concluded that "while some qualitative changes were noted in the islets,—such as an increase or diminution of the eosinophile cells, a granular change in the cells, atrophy of the cells with increase of the intercellular substance,—there were none which could be regarded as constant for any one experiment and constantly increasing with the duration of the experiment." Opie, Schulze, Diamare, and Jarotzky have arrived at similar conclusions, while Hansemann believes that the apparent increase during digestion is due to a more marked differentiation arising from the changes in the acini. The statement that prolonged stimulation of the

gland by overfeeding, or by the administration of pilocarpin, causes transformation of secreting acini into islands of Langerhans is based upon experiments carried out by Lewaschew in Heidenhain's laboratory. They have not, however, been confirmed by other observers. Statkewitsch, who has described alterations in the secreting acini in several specimens of animals under various conditions, thinks that they are merely the results of intense changes in the gland cells, and are not stages in a transition to cell islets. Jarotzky, as the result of his experiments, comes to the conclusion that the islands of Langerhans are independent structures, and are not connected with the altered gland acini met with as the result of altered dietetic conditions. He attributes the results obtained by Lewaschew to imperfect fixation. After the administration of pilocarpin Opie found that no increase in the number of cell islets could be detected, and that no transition stages between glandular acini and cell islet could be seen. He points out that in Lewaschew's experiments the normal variations in the number of islands in various parts of the gland, and in different glands, are not sufficiently taken into account.

The more powerful physiological stimulus afforded by injection of secretin has recently been employed by Dale in investigating this subject. He states that the prolonged administration of secretin produces changes in the gland cells of such a kind as to assimilate them in arrangement and properties to those forming the epithelium of the ductules and centro-acinar cells, thus bringing about reversion to an embryonic type. The lumina of the acini disappear and the cells are brought into more intimate relation with the blood-vessels. These altered masses of cells are regarded by Dale as being islands of Langerhans, and he states that numerous intermediate forms, retaining obvious traces of their former alveolar structure, can be found. He therefore agrees with

Lewaschew that the cell islets are not independent structures, but, as Laguesse has suggested, represent an internally secreting stage in the life of the pancreatic tissue. Further investigation of the subject by this method is, however, desirable before the true interpretation of the results described by Dale can be arrived at, and it is more particularly desirable that serial sections stained by appropriate methods should be examined, and that models prepared by the Born wax-plate method should be compared with those made from normal cell islets, for the evidence at present available cannot be regarded as conclusively demonstrating a structural connection of the secreting acini with the cell islets in the adult forms of the higher types of animals.

The experiments of Mankowski, in which the pancreas was ligatured in two places, were undertaken to disprove observations made by Schulze, in which it was found that the cell islets remained embedded in connective tissue, after the glandular acini had been destroyed as the result of the changes produced by tying the ducts. Mankowski's conclusions have not, however, been supported by the experiments subsequently undertaken by Ssobolew, Sauerbeck, Zunz, and De Witt, who confirmed the observations originally made by Schulze as to the atrophy of the gland tissue and preservation of the cell islands after ligature of the excretory duct of the gland.

Ssobolew also found that if portions of the gland are transplanted, the glandular parenchyma disappears, but the islands of Langerhans are extremely resistant and remain for long unchanged.

An interesting case has recently been carefully examined and described by S. G. Scott, in which a condition, similar to that induced experimentally in animals by ligature of the pancreatic duct, was brought about by an obstruction due to a malignant growth of the head of the gland. The body of the organ was markedly atrophied

and the duct was dilated. Under the microscope an extreme degree of fibrosis was found, and a number of cell-groups, which, in serial section, had the appearance and character of cell islets, were seen embedded in the fibrous tissue, but no secreting glandular tissue could be distinguished. There was no evidence of diabetes, and

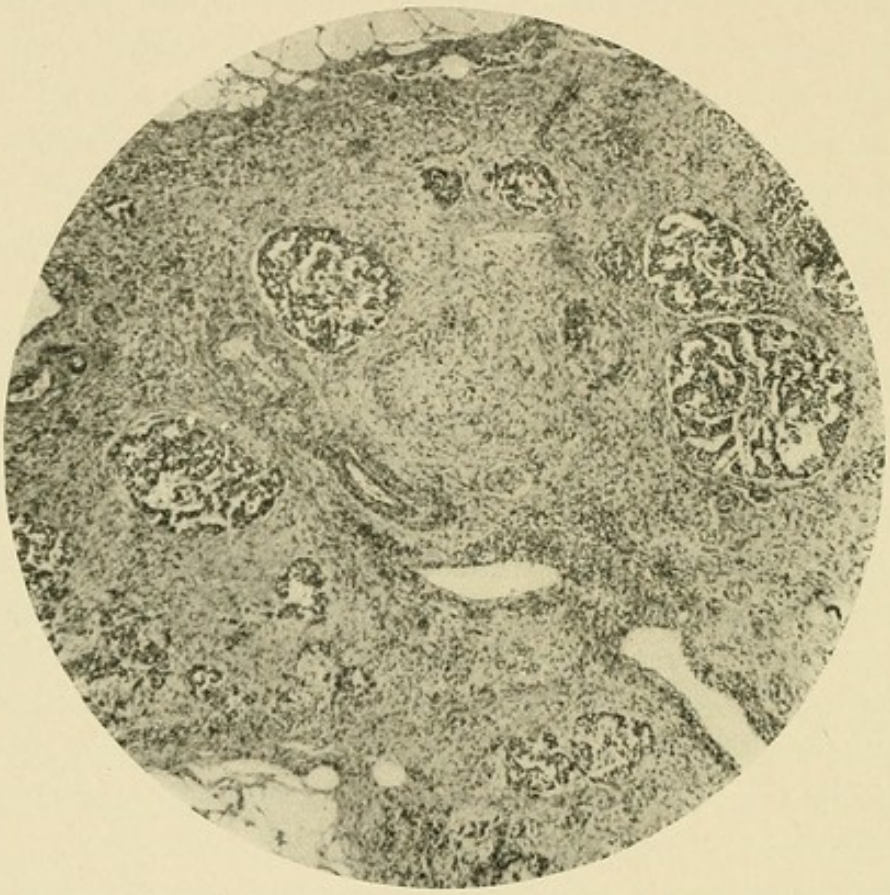


Fig. 47.—Obstruction of the pancreatic duct by carcinoma of the head of the gland, giving rise to atrophy and fibrosis of the body with persistence of the islands of Langerhans (Scott) (× ca 30).

the urine gave no reaction for sugar during life, in spite of the almost complete disappearance of the secreting parenchyma of the gland.

Some observers, basing their theory on the microscopical characters of the cells, have regarded them as lymphoid structures, but their origin from an embryonic

anlage, the arrangement of the cells, and their appearance in well-fixed preparations, at once differentiate them and suggest that such an opinion can only have originated from the study of imperfectly prepared specimens.

That they are not embryonal remains, as some have supposed, is shown by the fact that they exhibit no evidence of degeneration in adult life, and further that, although they appear to be more numerous in the embryo and in early life than in the adult, the disproportion is only relative and not absolute.

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CHAPTER VII

PHYSIOLOGY

The anatomical similarity of the pancreas to the salivary glands led the early observers to consider that their functions were also of the same nature, and it was not until Bernard pointed out, in 1849, that the pancreatic juice was concerned in the digestion of fats, and, in 1856, that it was also capable of acting upon proteid material, that the vastly greater importance of the pancreas as a digestive organ came to be recognized. The subsequent investigations of other workers upon the processes of digestion have shown that the pancreas is the digestive organ of the body *par excellence*, it is capable of dealing with all the chief forms of food material, its action is more energetic and complete than any other, and, moreover, it prepares for absorption substances, such as fat, which are little, if at all, changed by the secretions of the other digestive organs. The researches of Pawlow and his colleagues on the work of the digestive glands demonstrated in a masterly manner that the processes of digestion are not made up of a series of isolated phenomena, but that each step follows in an orderly manner as the result of the one which precedes it, and that to this rule the pancreas furnishes no exception. A study of the mechanism of the pancreatic secretion by Bayliss and Starling has resulted in the enunciation of a new principle concerning the co-ordination of its digestive functions with those of other parts of the alimentary tract, which has opened up a fresh field for research, and promises to throw light upon a number of hitherto obscure problems in other regions of the body.

Although the digestive functions of the pancreas are undoubtedly of great importance in the due maintenance of the health of the organism, there is reason to believe that it exerts a still more important influence upon the internal metabolism, particularly through the control it exerts upon the assimilation of carbohydrate material by the tissues. The salivary glands, stomach, and intestinal bacteria may to a certain extent replace or supplement its digestive work, but, so far as we know at present, no other organ can take on its functions in carbohydrate metabolism.

Analyses of the pancreas by Oidtmann show that it consists of 74.53 per cent. of water, 24.57 per cent. of organic matter, and 0.95 per cent. of inorganic substances. The same observer found in the salivary glands of the dog 79 per cent. of water, 20 per cent. of organic and 1 per cent. of inorganic matter. The organic matter of the pancreas consists of proteids (albumin, globulin, and nucleo-proteid), zymogens, nuclein, leucin, xanthin (1.8 p. m.), hypoxanthin (3 to 4 p. m.), guanin (2 to 7.5 p. m.), adenin, inosit, lactic acid, volatile fatty acids, and fat. The principal constituent of the cells, however, appears to be a complex nucleo-proteid, which Hammarsten regards as identical with trypsin. This when boiled gives a coagulated proteid and a phospho-gluco-proteid, and the latter on treatment with dilute acid yields a reducing substance having the characters of a pentose. Although small quantities of a pentose (l-xylose) can be obtained from most organs in the body, the pancreas yields over four times the proportion that can be obtained from any other structure. Neuberg found 2.48 per cent. of the dry weight of the pancreas was xylose, while from the liver and from the thymus only 0.56 per cent. could be obtained, the submaxillary gland yielded 0.53 per cent., the thyroid 0.5 per cent., and the kidneys, spleen, brain, and muscles under 0.5 per cent.

During life the organ is alkaline in reaction, but it very rapidly becomes acid after death; at the same time small quantities of tyrosin make their appearance.

Activity of the pancreas has been shown by Barcroft and Starling to be accompanied by an increased oxygen absorption, which is not due to the augmented blood-flow through the organ. Normally the oxidation in the pancreas is greater than in the body generally, being about the same as in the submaxillary gland. Increased metabolism in the pancreas has been found by Bainbridge to be accompanied by increased lymph formation, and he has shown that there is a close relation between the secretion of pancreatic juice and the increased flow of lymph.

The **mechanism of the flow of the pancreatic secretion** was first satisfactorily studied by Pawlow, by a method of obtaining the juice under practically normal conditions, which he described in 1879. In this method, which differs only slightly from that reported by Heidenhain in the following year, an oval piece of the duodenal wall containing the orifice of the pancreatic duct is cut out, and, after the lumen of the bowel has been restored, is brought to the surface and stitched into the slit in the abdominal wall. The wound heals quickly, and, after two weeks, when the animals are ready for observation, shows a roundish elevation of mucous membrane in which the cleft-like orifice of the duct appears about the centre. By paying strict attention to cleanliness, regulating the diet, and adding a certain quantity of sodium bicarbonate to their food, to make up for the loss of alkali through the pancreatic fistula, such animals can be kept in good health for a lengthy period. Pawlow's method overcame the difficulties which had beset attempts to investigate the mechanism and rate of secretion of the pancreatic juice under varying conditions by previous experimenters, for it allowed sufficient time for the animal to recover from the effects of the operation and the transitory interference

with its functions which had been found to result from the formation of a temporary fistula, while the inflammatory changes which followed the older methods of forming a permanent fistula were likewise avoided.

Employing dogs, provided with a pancreatic fistula in this manner, Pawlow investigated the effects of stimulating the nerves going to the pancreas, and results of variations of diet upon the secretion. He found that if the vagus in the neck be cut and left under the skin for four days, so that the cardiac fibres may degenerate, stimulation by a slow induced current, or by mechanical blows, causes a gradually increasing flow, after a latent period of three minutes. When the stimulation of the nerve is discontinued the flow does not cease at once, but continues in diminishing amount for four to five minutes. This part of the experiment can be done without an anæsthetic, thus avoiding any disturbing influences which might thereby be introduced. A slow induced current was employed, as it does not stimulate the vaso-constrictor nerves, excitation of which would diminish the blood supply and stop the secretion. If instead of resecting the vagus it is exposed and at once stimulated below the origin of the cardiac branches, after the cervical spinal cord had been cut to prevent reflexes from the sensory nerves, a similar flow of pancreatic secretion follows. In this so-called "acute method" it was found that simultaneous stimulation of the opposite vagus often had an inhibitory action, suppressing the secretion after a latent period, and that stimulation of the sympathetic at first slightly increased the amount of secretion, but soon brought it to a standstill. As the result of these experiments Pawlow came to the conclusion that the mechanism of the pancreatic secretion is arranged upon the same plan as that of the stomach and salivary glands, being determined reflexly, or psychically, through the cortex by impulses leaving the central

nervous system and travelling by way of the vagi and splanchnic nerves to the gland. The failure of Heidenhain and other observers to obtain a flow of pancreatic juice on stimulating the vagi and splanchnic nerves was attributed by him to the unphysiological conditions under which their experiments were carried out.

A pupil of Pawlow, Popielski, found that the introduction of acid into the duodenum brought about a flow of pancreatic juice after section of both vagi and splanchnics, or destruction of the spinal cord, or complete extirpation of the solar plexus, and came to the conclusion that there were local centres presiding over the secretion in the scattered ganglia of the pancreas, and that, since there was no secretion if the duodenum was cut across a short distance from the stomach, the most important part was situated near the pylorus. Wertheimer and Lepage confirmed Popielski's observation with regard to the effect of acid in the duodenum, and further reported that a similar result followed the introduction of acid into the jejunum, but that the intensity of the reaction diminished as the distance from the duodenum increased. This they endeavoured to explain by suggesting that the local centre for the duodenum lay in the pancreas, but that for the jejunum was probably situated in the solar plexus. These observers, in their attempts to unravel the problem of the means by which the acid produced its effect, also found that if it were injected directly into the circulation no secretion of pancreatic juice ensued.

The most serious defect of Pawlow's method of investigation was one against which he had guarded in his researches into the secretory mechanism of the stomach. In his experiments upon the gastric secretion he provided against the entry of food into the stomach by an œsophageal fistula, but no provision was made to guard against the entry of acid chyme from the stomach into the duode-

num in the pancreatic experiments. This, however, has been shown by the researches of Bayliss and Starling to be the most important, if not the only stimulus that induces the flow of pancreatic juice. Pawlow and his fellow-workers were well aware that the introduction of dilute hydrochloric acid into the duodenum brought about active secretion, so much so in fact that they made use of it as a crucial test for deciding the normal relation of the alimentary canal to the pancreas, but their minds were so imbued with the idea of a nervous control that they failed to recognize the true importance of their own observations in this direction. They attributed the result produced by the acid to excitation of the peripheral nerve-endings in the mucous membrane of the intestine. A second hypothesis considered by Pawlow, only to be rejected, was that the acid was absorbed into the blood and carried to the secretory centres or gland cells, where it acted as a stimulant for the production of the secretion. His reasons for setting aside this explanation were that if it were correct, the alkalinity of the blood would be diminished during digestion and not increased, as it is known to be; further, that experiment shows that when acid solutions are injected into the rectum the pancreas remains at perfect rest, and in the same way acids do not act upon the pancreas so long as they remain in the stomach.

A third explanation has been offered by Bayliss and Starling and supported by convincing experimental evidence. After setting aside the nervous theory, by proving that the presence of hydrochloric acid in a ligatured loop of the upper part of the jejunum, the nervous connections of which had been completely destroyed, brought about a copious flow of pancreatic juice, and, accepting the observations of Wertheimer, that the introduction of acid into the blood failed to excite secretion, they concluded that the acid must act upon the cells of

the intestinal mucous membrane and produce some substance which, being absorbed into the blood, travels to the pancreatic cells and arouses them to activity. To prove this they scraped off the cells lining the mucous membrane of the upper part of the jejunum, rubbed them up in a mortar with sand and 0.4 per cent. hydrochloric acid, filtered the extract, and injected the filtrate into a vein. The result was a brilliant confirmation of their surmise, for a flow of pancreatic juice was produced which was even greater than that excited by the introduction of acid into the lumen of the intestine. This effect was

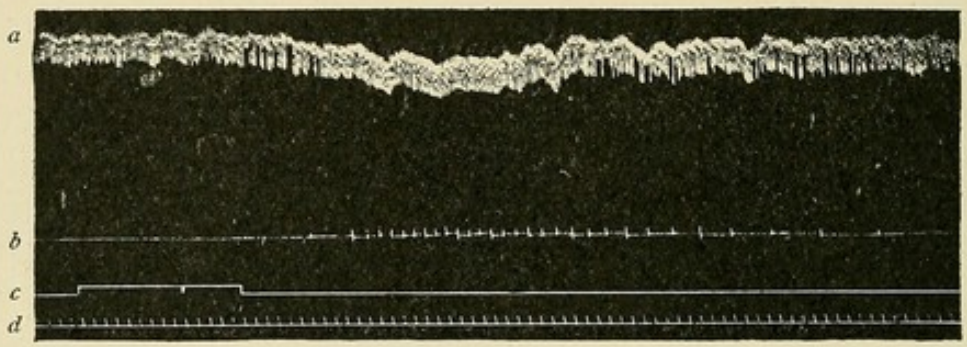

Fig. 48.—The effects produced by the injection of acid into a loop of small intestine after destruction of the nerves: *a*, Blood pressure; *b*, drops of pancreatic juice; *c*, signal marking injection of 50 c.c. of 0.4 per cent. HCl; *d*, time in ten minutes (Starling).

found not to be specific, for an extract prepared from the upper part of the intestine of any vertebrate animal induced pancreatic secretion in the same, or any other, species into which it was injected. The activity of the extract prepared from various parts of the intestine was shown to diminish as the distance from the pylorus was increased, that from the duodenum being most active and that from the lower part of the ileum being entirely ineffective, thus agreeing with the observations of Wertheimer and Lepage on the secretory activity induced by the introduction of acid into various parts of the gut.

The chemical messenger, or harmone, which brings

about this reaction, and to which its discoverers have given the name of "*secretin*," has not been isolated. Once formed by the action of acid, or boiling water, on the intestinal mucous membrane, it can be boiled, showing that it is not a ferment, neutralised or made alkaline, without being destroyed. It is readily oxidized, is not precipitated by the ordinary reagents for proteids, but is soluble in 90 per cent. alcohol in the presence of ether, although it is insoluble in absolute alcohol and ether.

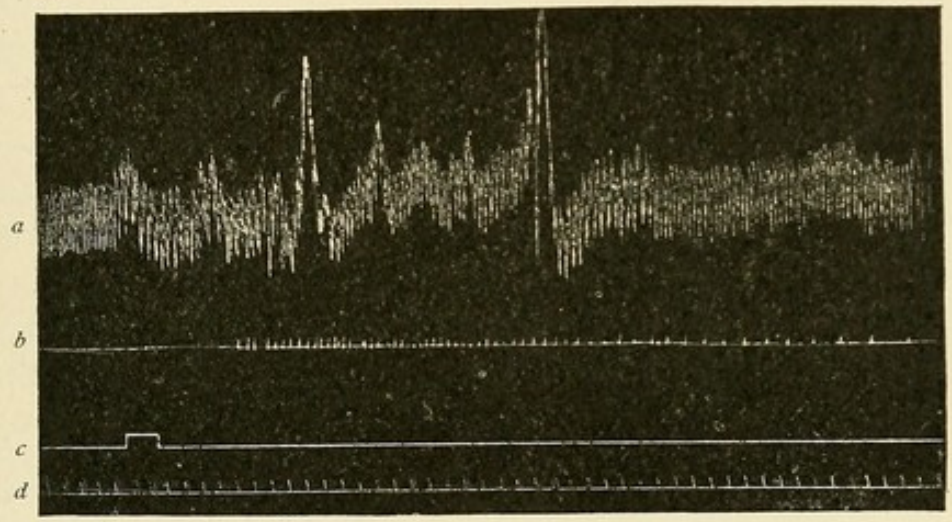

Fig. 49.—Effects produced by the injection of secretin prepared from the intestinal mucous membrane: *a*, Blood pressure; *b*, drops of pancreatic juice; *c*, signal marking injection of secretin; *d*, time in ten minutes (Starling).

It is diffusible through animal membranes, and can be filtered through a gelatinised Chamberland filter. It is not precipitated by tannic acid, thus excluding bodies of an alkaloidal nature and di-amido compounds. This evidence points to secretin being a body of relatively small molecular weight, and not a colloid. It may be compared to the active principle of the suprarenal gland, adrenalin, which has been obtained in a crystalline form and the chemical constitution of which has been determined. This is indeed what might be expected of a

substance which has to be turned out into the blood at repeated intervals in order to produce in some distant organ a physiological response proportional to the dose.

Even after coagulation of the mucous membrane by heat or alcohol, secretin can be extracted by the action of warm dilute acid, but mere extraction with water or alcohol, in which secretin is freely soluble, does not give an active solution. It is therefore concluded that the epithelial cells contain a precursor of secretin, which is insoluble in water, alcohol, and salt solution, termed "*pro-secretin*," and that this, on hydrolysis with acids, gives rise to the active substance. It has been found impossible to prepare secretin, or a substance having a similar action on the pancreas, from any organ or tissue of the body other than the mucous membrane of the duodenum and the jejunum. The effect of secretin appears to be limited to the pancreas and liver, for while a solution, free from bile salts, on injection into a vein induces a marked flow of pancreatic juice and some increase in the excretion of bile, it is found to have no action upon any other gland. Bayliss and Starling believe that it acts as a direct chemical stimulant to the secretory cells of the pancreas, since the flow of secretion is still obtained when the gland has been cut off, as far as possible, from all nervous connections.

The question as to whether secretin can be produced from the mucous membrane of the upper part of the small intestine by any other substance than hydrochloric acid, which is undoubtedly the most effective, has received attention at the hands of several observers. Fats were believed by Pawlow to be independent excitors of the pancreatic flow, for he pointed out that, since they restrain the secretion of gastric juice, the output of pancreatic juice which follows their administration is not likely to be indirectly due to acid in the gastric contents. Oil when rubbed up with duodenal mucous

membrane does not give rise to secretin, but Fleig has shown that if a solution of soap is employed instead, the mixture, on injection into the blood stream, gives rise to active pancreatic secretion. It is therefore possible that fats owe their activity as excitors of the pancreatic secretion to the formation of a certain amount of soap in the intestine, which in its turn sets free secretin. Fleig regards the secretin produced by the action of soap as different from that formed by acid, and has named it "*sapocrinin*," but there is no evidence to justify such a conclusion.

Irritating substances such as oil of mustard, or ether, do not produce secretin from the scraped-off mucous membrane (Starling), but they produce a flow of pancreatic juice on being introduced into a loop of small intestine, which Wertheimer's experiments show is due to the presence of secretin in the blood. Starling explains this by supposing that the secretin is formed by a process of hydrolysis in the over-stimulated cells of the intestine, possibly as a stage in their death.

Most investigators have admitted that secretin is the most important exciter of the pancreatic secretion, but there are some who still believe that nervous activity plays some part in the process. Starling considers it doubtful whether the vagus has any direct secretory action on the cells of the pancreas, and points out that the normal effect of stimulating the vagus is to bring about movements of the stomach, which may cause its contents to flow into the duodenum, and there set up the chemical mechanism of secretion which he and Bayliss discovered. When due precautions are taken to prevent the stomach contents passing into the intestine, stimulation of the vagus produces such a slight flow from the pancreatic duct that it can hardly be regarded as evidence of the presence of secretory fibres in the nerve. Some

observations on the pancreatic secretion in a man have been described by Clayton-Greene, which he thinks support Pawlow's original theory that secretion is influenced by a nervous mechanism. The case was one in which, during pylorectomy for malignant disease of the stomach, a portion of the pancreas was torn across, and three days later a pancreatic fistula formed. Food given by the mouth was followed, some few seconds after it had been swallowed, by a definite secretion of pancreatic juice, and the sight of food was also found to set up secretion. He considers that the conditions under which the flow started were such that it could not be explained as the result of the formation and absorption of secretin, and that in the observations made in this case there was support for the theory that stimulation of a sensory nerve could evoke a secretion from the pancreas as it does from the salivary glands.

The **composition and characters of the external secretion of the pancreas** have been chiefly studied in dogs. That obtained by inserting a cannula into the duct two or three hours after a meal is found to be a clear, odourless, colourless, syrupy fluid of a strongly alkaline reaction and a specific gravity of about 1.030. It contains from 2 to 15 per cent. of solid matter, of which a variable, but often considerable, proportion is coagulable proteid. The alkalinity, which is equal to 0.2 to 0.4 per cent. of sodium hydrate, is generally said to be due to carbonates and phosphates of sodium. Alkaline chlorides, and small quantities of calcium and magnesium phosphates, leucin, fat, and soaps are also present. The fluid readily decomposes on exposure to the air. The following analyses of the temporary secretion, obtained directly after operation by Schmidt, show that in the same form of fistula the proportion of total solids varies very considerably:

	(*a*)	(*b*)
Water	900.8	884.4
Total solids	99.2	115.6
Organic matter	90.4	..
Ash	8.8	..

The secretion from a permanent fistula, collected a few hours to several days after the operation, resembles that from a temporary fistula in its general characters, but is poorer in solids and coagulable proteid. It contains from 1.5 to 3.5 per cent. of the former and 0.5 to 2.5 per cent. of the latter. The specific gravity is also less, being generally about 1.010 to 1.011. Schmidt's analyses of three specimens gave the following results:

	(*a*)	(*b*)	(*c*)
Water	976.8	979.9	984.6
Total solids	23.2	20.1	15.4
Organic matter	16.4	12.4	9.2
Ash	6.8	7.5	6.1

Starling states that the juice from a permanent fistula, after feeding, is similar in all respects to that flowing from a temporary fistula as the result of injecting secretin, or introducing acid into the duodenum. According to him, it is a somewhat viscid, clear, colourless fluid, of a specific gravity of about 1.030, and contains from 2 to 3.5 per cent. of total solids. About 1 per cent. of the solid consists of salts and the remainder of coagulable proteid. It is always strongly alkaline, 10 c.c. of the juice requiring from 10 to 15 c. c. of decinomal acid to neutralise it. That is to say, its alkalinity is equivalent to from 0.365 to 0.547 per cent. of hydrochloric acid, figures which correspond closely to the acidity of the gastric juice (0.48 per cent.). A certain proportion of the proteid is precipitated on neutralisation. In neutral solu-

tion about half the total proteid is coagulable at between 55° and 60° C., the remainder coagulating at about 75° C.

Opportunities for studying human pancreatic juice are rare, and even in such cases as have occurred the material can hardly be regarded as normal, for it has usually been either the contents of a cyst or the drainings from a wound. In a case where the entry of the secretion into the intestine was prevented by the pressure of a malignant growth upon the duct of Wirsung, Herter found that it was a clear, alkaline fluid, without odour, and contained 2.41 per cent. of solids, of which 0.64 per cent. was soluble in alcohol. He separated 1.15 per cent. of peptone (and enzymes), but no other proteid, and 0.62 per cent. of mineral substances. The ash was found to be very rich in alkaline phosphates. Zawadsky analysed the pancreatic secretion of a young woman with a fistula that remained after a cyst of the pancreas, and found 864.05 p. m. of water, 132.51 p. m. of organic matter, and 3.44 p. m. of inorganic substances. The quantity of proteid was 92.05 p. m. The investigations reported by Glaessuer, on a case operated on by Körte, in which the pancreatic duct and common bile-duct were drained for eight days after an operation undertaken to relieve a simple stricture of the bile-passage following duodenal ulcer, will be referred to later, when the functions of the pancreatic juice are considered, but it may be mentioned here that the fluid was clear, alkaline in reaction, and of a specific gravity of 1.007. It contained 6 per cent. of ash and 15 per cent. of proteid, of which more than half was albumin.

Different observers vary considerably in their estimate of the total daily output of pancreatic juice. Bidder and Schmidt state that the dog, under normal conditions, secretes 2.5 grams per kilo of body-weight a day, while Pawlow gives 21.8 c. c. per kilo as the normal output for twenty-four hours. On the basis of Bidder and

Schmidt's findings an average man of 154 pounds weight might be expected to secrete 175 grams of pancreatic juice a day, but in Glaessuer's case the daily amount collected was from 500 to 800 c.c., and in Wohlgemuth's 400 c.c. It is generally assumed that the amount lies between 200 and 500 c.c.

Excepting in herbivora, such as the rabbit, in which digestion is uninterrupted, the secretion of pancreatic juice is intermittent. In a dog with a pancreatic fistula there is no secretion while the animal is fasting, but the administration of food, or even the sight of food, brings about a flow, after a latent period of two to three minutes. The flow of secretion induced by a meal gradually increases in amount until it reaches a maximum in two to three hours; it then diminishes, the lowest reading being reached in five to seven hours; a second rise, reaching its maximum in the ninth to the eleventh hour, may then take place, after which it again gradually sinks until it finally stops about the eighteenth to the twentieth hour, unless a fresh supply of food is ingested. Both the amount and rate of secretion have been shown by Pawlow to vary with the nature of the food. Walther, working in Pawlow's laboratory, found that, taking the hourly quantity of pancreatic juice poured out for corresponding nitrogen equivalents of flesh, bread, and milk, the following results were obtained:

With 100 grams of flesh	38.7	44.6	30.4	16.9	0.8	. .	. .	. .	131.45 c.c.
With 250 grams of bread . . .	36.5	50.2	20.9	14.1	16.4	12.7	10.7	6.9	168.4 c.c.
With 600 c.c. of milk	8.5	7.6	14.6	11.2	3.3	1.0	. .	. .	46.1 c.c.

When these results are plotted out in curves the variations in amount and rate of secretion induced by the food materials experimented with are well seen (Fig. 50).

Wohlgemuth, working with a patient with a pancreatic fistula the result of an operation after injury of the pancreas, also found that, employing fixed quantities of food and collecting the juice from hour to hour, the quanti-

tity secreted was greater with carbohydrates, smaller with albumin, and least with fats. The secretion was usually most active in the second hour.

According to the secretin theory, the variations produced by different classes of food material are not due, as Pawlow supposed, to some specific influence they

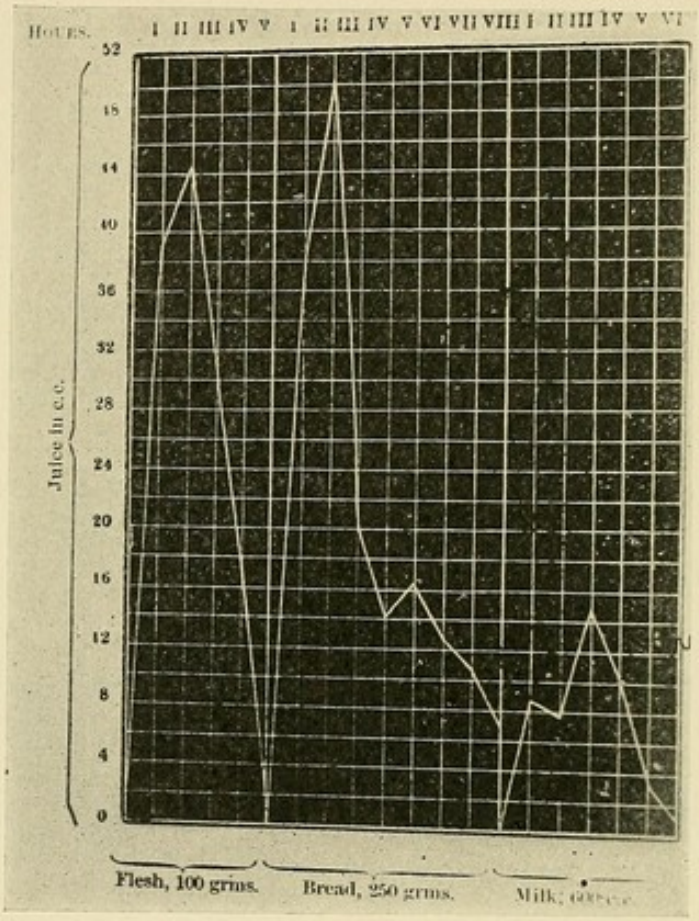

Fig. 50.—Curves of secretion of pancreatic juice after 100 grams of flesh; 250 grams of bread; 600 c.c. of milk (Pawlow).

exert upon the pancreas by way of its nerve supply, but upon the acidity of the chyme and its rate of discharge into the intestine. The first portion of the acid stomach contents passed into the duodenum will continue to excite the formation of secretin from the epithelial cells until the alkaline pancreatic juice, secreted in re-

sponse to its stimulating effect, has completely neutralized the acid; a second supply of chyme will then be ejected by the stomach, giving rise in its turn to the formation of secretin and of an alkaline pancreatic juice by which it will be neutralised, and this process will be continued so long as the products of the activities of the stomach continue to pass into the intestine. As a certain amount of bile is secreted at the same time as the pancreatic juice, and the secretions of the intestine are also alkaline, a somewhat smaller quantity of pancreatic juice will be formed than would, by itself, be sufficient to neutralise the acid contents of the stomach.

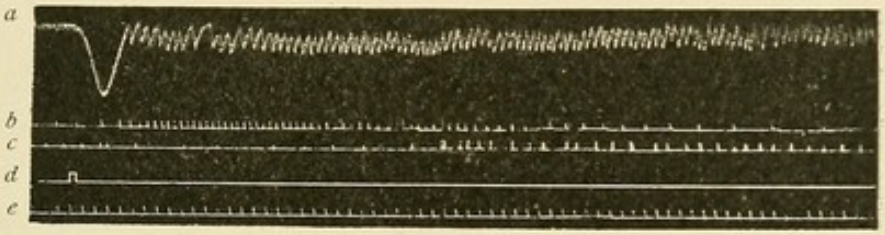

Fig. 51.—Effects of the injection of secretin on the flow of pancreatic juice and bile: *a*, Blood pressure; *b*, drops of pancreatic juice; *c*, drops of bile; *d*, signal marking injection of secretin; *e*, time in ten minutes (Starling).

Ferments.—The pancreatic juice contains four, or possibly five, ferments or digestive enzymes: (1) "Amylopsin," or pancreatic diastase, a diastatic ferment which converts starch and glycogen into dextrin and maltose. (2) "Trypsin," a proteolytic ferment which converts proteids into albumoses, peptone, and amino-acids. (3) "Steapsin," or "pialyn," a steatolytic, lipolytic, or fat-splitting ferment, which converts neutral fats into fatty acids and glycerine. (4) A milk-curdling ferment, which in the presence of calcium salts changes caseinogen into casein; and, possibly, (5) a ferment which has been named "lactase," because of its supposed power of splitting milk-sugar into galactose and dextrose.

The collective pancreatic ferments are thus capable

of acting upon all forms of food-stuffs and carrying to a final issue the changes commenced by other digestive glands. The same ferments are found in the pancreatic secretions of all vertebrates, but in the human subject, although trypsin is present during the last third of fœtal life, the diastatic ferment does not make its appearance until a month or more after birth.

The process of digestion of starches commences in the mouth through the agency of the ptyalin of the saliva, but it is quickly, although not immediately, stopped in the stomach through the precipitation of the diastatic ferment by the gastric juice. In the intestine the amylopsin of the pancreatic secretion continues the process, but much more vigorously and rapidly, exerting some action even upon unboiled starch. The main results of the activity of the two ferments are the same, however—namely, dextrin and maltose. Only small quantities of dextrose are produced, even by the action of the more vigorous pancreatic ferments. The final conversion to this substance is brought about either through the activity of epithelium of the intestinal wall or, possibly, by the action of a special ferment in the pancreatic juice, to which the name "maltase" has been given. The diastatic ferment of the pancreatic juice acts most satisfactorily at a temperature of 30° to 45° C. in a neutral or very faintly acid medium. The optimum reaction, according to Melzer, is about 0.01 per cent. of hydrochloric acid. It is quickly destroyed by strong mineral acids and its action is suspended by 0.05 per cent. of lactic acid or 0.08 per cent. of acetic acid (Hofmeister).

Although Claude Bernard discovered the digestive powers of pancreatic juice upon proteids, he believed that the presence of bile was necessary, and it was not until Coivisart, in 1857, demonstrated that the juice alone exerted a powerful solvent action at the temperature of the body, and that infusions of the fresh gland possessed

the same property, that our knowledge of this function of the pancreas was placed on a secure footing. The latter observer also showed that the products of the pancreatic digestion of proteids had the same general characters as those resulting from the action of gastric juice. In 1877, Kühne carried the investigations a step further by excluding the effects of bacterial action, of which account had not been taken by previous experimenters. He found that the addition of a small quantity of salicylic acid to a pancreatic digestion-mixture prevented the growth of micro-organisms but did not stop the digestive process. He therefore concluded that the action was due to an enzyme and named it "*trypsin.*" It is now known that the pancreatic juice does not contain trypsin but trypsinogen, and that it is by the action of a substance contained in the succus entericus, known as "*enterokinase,*" on the latter that the active ferment is produced. Different views are held as to the nature of enterokinase. By its discoverers, Pawlow and Schepowalnikow, it is regarded as a "ferment of ferments," and in this they are supported by Starling, but Delezenne, and others of the French school, consider that it is rather of the nature of an amboceptor binding the ferment to the proteid. Delezenne has recently stated that inactive pancreatic juice acquires an extremely powerful proteolytic action on being incubated for several hours with a suitable quantity of a soluble calcium salt; barium, strontium, and magnesium have little or no effect and the action of lime salts in this respect is specific. Julius Wohlgemuth has also shown that the trypsinogen contained in the juice from a fistula is activated by glycine, alanine, and leucine, and feebly by tyrosine.

Schiff, Herzen, Gachet, and Pochon have maintained that the spleen is of importance in the production of trypsin, but their conclusions have been disputed by Ewald and Heidenhain, and are not generally accepted.

The proteolytic ferment of the pancreatic juice can act in an alkaline, neutral, or faintly acid medium. The optimum is about 1 per cent. of sodium carbonate, other alkaline carbonates being found to be much less effective. Its action is prevented by the presence of free mineral acids, even in small quantities. Free hydrochloric acid destroys the ferment more rapidly if pepsin is also present, but hydrochloric acid combined with albumin, in not too large amounts, appears to rather increase the rapidity of its action. Organic acids exert a much less harmful effect than mineral acids, and it is said that in the presence of 0.2 per cent. of lactic acid, bile, and salt, the proteolytic action is very energetic. According to Wohlgemuth, the tryptic activity of pancreatic juice is doubled by the presence of bile. Small quantities of salicylic acid have no effect, and only saturated solutions interfere with its activity. The nature of the proteid also exerts some influence on the ease with which the digestive process proceeds; fresh unboiled fibrin is attacked and dissolved exceedingly rapidly, but boiled fibrin or coagulated white of egg are digested much more slowly, hence it is advisable to employ one or other of the latter when testing the digestive power of a fluid containing pancreatic ferments. The optimum temperature for the action of trypsin lies between 30° and 45° C. Beyond that its digestive power rapidly increases up to 60° C., but the ferment is at the same time quickly destroyed and loses its power, so that at 75° to 80° C. it ceases altogether.

On exposing a proteid to the action of activated pancreatic juice it is found to be attacked and eroded from the outside, without undergoing any swelling, or becoming clearer, as in gastric digestion. The alkali albumin first formed, when the digestion takes place in an alkaline medium, is quickly converted into deuteroalbumose; this in turn gives rise to peptone, and from this again various amino-acids, and relatively simple nitrogenous

bodies, are derived. No proto-albumose or hetero-albumose can be detected, as in the earlier stages of gastric digestion, probably because the action of trypsin is so much more rapid and energetic than that of pepsin that these bodies are broken down as quickly as they are formed. Kühne as the result of his work on digestion considered that the peptone formed in the stomach differed from that produced in pancreatic digestion. The former he named "amphopeptone," because he believed that it consisted of two united groups ("hemi-peptone," which could be broken down by trypsin into simpler bodies, and "antipeptone," which was resistant to the action of trypsin); the latter, he stated, consisted only of "antipeptone." Kühne himself, however, had doubts as to the unity of antipeptone, and it has now been shown that it is really a mixture of various amino-acids and hexone bases. Emil Fischer, working at the cleavage products of proteid digestion, has isolated combinations of amino-acids, which he terms "polypeptides," occupying an intermediate position between the proteoses and peptones, on the one hand, and the final products of digestion on the other. It is now generally accepted that "ampho-peptone," "hemi-peptone," and "anti-peptone," in the sense used by Kühne, do not exist, and that there is no essential difference between the products of the activity of trypsin and of pepsin. Both split up the proteid molecule by a process of hydrolysis into simpler combinations of a similar nature, but while the whole series of processes is rapidly and easily performed by the powerful tryptic ferment, the gastric juice only acts completely upon a variable fraction, which can be broken off with comparative ease. The small quantities of leucine, tyrosine, and other bodies of low molecular weight, now known to be formed during gastric digestion, are what were grouped together by Kühne as anti-peptone. The only essential difference, therefore, between the

proteolytic activity of trypsin and pepsin is in their velocity of action.

It was formerly believed that the leucine, tyrosine, and similar bodies of relatively simple composition produced during the digestion of proteids, were merely waste substances formed by the excessive activity of the pancreatic juice, which were normally conveyed to the liver and there rapidly destroyed, but evidence is now rapidly accumulating which tends to show that the main part of the proteid taken in as food is broken up into these simple cleavage products before it is absorbed, and that the body proteids are built up synthetically from them. That it is possible to maintain the weight, health, and nitrogenous equilibrium of animals by feeding them on the crystalline cleavage products of the pancreatic digestion of proteids has been experimentally demonstrated by Loewi and others, and the probability that such is the natural process by which proteids are absorbed does away with the difficulty of explaining how the constant chemical composition of the various tissues of the body is maintained in spite of the widely differing nature of the food materials from which they are derived.

Fresh pancreatic juice, which has not been activated by enterokinase, possesses slight digestive powers for proteids. This action, which is quite distinct from that due to trypsin, is akin to the feeble proteolytic property possessed by many animal tissues, particularly the kidney (Vernon).

Cohnheim has demonstrated the presence of a ferment in the succus entericus of the dog, which has the property of splitting proteoses and peptone into simpler products, but has no action on native proteids, and to it he attaches considerable importance. According to Kutscher, however, it is a comparatively feeble and unimportant ferment. To this intestinal enzyme Cohnheim gave the name of "*erepsin*," but the same term has also been used

by Starling to describe the proteolytic ferment met with in fresh pancreatic secretion and in the tissue juices generally. A similar ferment, found in the intestinal juice of suckling infants, may possibly be of value, as it is said to speedily break up caseinogen into casein.

Collagen, the chief constituent of connective tissue, is not acted upon by pancreatic juice, unless it has previously been boiled with water, or has been acted upon by dilute acid, hence connective tissue is not digested if the stomach has been removed, or if the secretion of acid is interfered with by disease. Gelatin ingested as such, or derived by previous digestive changes from collagen, is converted by trypsin into gelatin-peptones. Elastin is attacked and dissolved. Mucin and nucleo-proteids, after a preliminary cleavage into their constituent proteids and organic radicles, undergo digestive changes in the pancreatic secretion. In the fasting animal a mixture of pancreatic juice with the intestinal secretions is said to exert an exceedingly powerful action upon the wall of the intestine, giving rise to extensive inflammatory changes and erosions (Starling).

The **digestion of fat** is peculiarly a function of the pancreatic juice. Neutral fats are entirely unaffected by the secretions of the salivary glands, and in the stomach are only slowly changed, yielding but 1.0 to 2.7 per cent. of fatty acid after some hours. Fine emulsions of fat, such as occur in the yolk of eggs and in milk, may be more completely digested, however, for Volhard found that the former, after one to four hours' stay in the stomach, might contain as much as 78 per cent. of free fatty acid, a fact probably of some practical importance in young infants before the lipolytic function of the pancreatic secretion is fully developed, and in adult patients whose pancreas is disorganised by disease. The fat-splitting power of the stomach is believed to be due to a gastric lipase, although it has also been attributed to the

action of bacteria. No fat-splitting ferment has been obtained from the intestinal mucous membrane or from the chyle.

Eberle, in 1834, was the first to observe that pancreatic juice had the power of emulsifying fat, but it was Bernard who, in 1849, discovered that it had the property of splitting fats with the liberation of fatty acids.

The steapsin of the pancreatic juice is much less stable than the tryptic and diastatic ferments. It is very susceptible to the action of acids, being quickly destroyed by all except the higher fatty acids. Strong alkalies also affect it unfavourably. It is most active in a neutral or weakly alkaline medium, even 0.25 per cent. of sodium carbonate retarding its activity. Unlike the other pancreatic ferments, it is insoluble in water and in glycerine, so that its effects can only be studied by employing the fresh gland or the secretion, but that it is an enzyme is proved by its being destroyed on boiling and by its activity being maintained in the presence of antiseptics.

The digestive power of the pancreatic juice for fats is considerably increased by the presence of bile, and still more by the presence of bile and hydrochloric acid. Bile of itself has little or no digestive power, but a mixture of bile and pancreatic juice can digest more than three times as much fat as the pancreatic solution alone. According to the experiments of Wohlgemuth, the lipase of the pancreatic juice exists partly in an inactive form, and this is activated by the accession of bile. The enzyme acts best at the temperature of the body, and, although more vigorous at higher temperature, up to a certain point, is quickly destroyed, like the other ferments of the secretion.

Different views have been held from time to time as to the exact part the pancreatic secretion plays in the digestion and absorption of fat. Although Bernard discovered the saponifying action of pancreatic juice upon

neutral fats, he did not attach much value to it, but described a "ferment emulsif" to which he attributed the chief importance in the preparation of fats for absorption. Brücke, however, found that the presence of a certain amount of free fatty acid was sufficient to emulsify the remaining neutral fat, and arrived at the conclusion that the chief function of the fat-splitting ferment of the pancreatic juice was probably to provide the fatty acid for that purpose. Rachford has shown that under favourable conditions a sufficient amount of fatty acid is formed in the presence of bile and hydrochloric acid at room temperature to form a spontaneous emulsion in two minutes, thus explaining Bernard's results without invoking the aid of any special emulsifying ferment. In consequence of these and other observations it was held that only a small proportion of the ingested fat is split up into fatty acids and glycerine, and that this, aided by that naturally present in most fatty foods, converts the remainder into a fine emulsion which is absorbed by the intestinal epithelium and passed to the lacteals. The structure of the epithelial cells is not, however, suited for such a function, and fat globules have not been observed in their broad striated border, so that it is highly probable that the fat passes through the walls of the cells in a soluble form and is afterwards thrown down in visible particles. Zawarykin's suggestion that the fat is absorbed from the intestine by lymph cells and carried by them to the lacteals has been discredited, as also has the theory of Munk that a considerable portion of the fat is absorbed as emulsified fatty acids. It is now generally acknowledged that fat is absorbed in the form of soluble soaps, although in some animals a certain portion may also leave the intestine as dissolved fatty acids. The neutral fats in the intestine are believed to be split up by the action of the pancreatic juice into fatty acids and glycerine; the fatty acids then unite with the sodium,

potassium, calcium, and magnesium of the intestinal juices to form soluble alkaline soaps, and these are absorbed, together with the glycerine, by the epithelial cells of the intestinal wall, within which they are again synthesised to form neutral fat. Müller has shown that the macerated pancreas of the pig can split 86.4 per cent. of the fat of milk in twenty-four hours, and Rachford states that the steapsin of the pancreatic juice is probably quite capable of splitting up all the fats of a full meal in the time digestion usually takes within the body. Radziejewski has also proved that alkaline soaps are absorbed by the intestine, and Perewoznikoff has demonstrated that alkaline soaps and glycerine are synthesised to neutral fats. The presence of bile makes the free fatty acids, which are entirely insoluble in water, soluble, and increases the solubility of the alkaline soaps. Its solvent power is greatly augmented by the presence of lecithin, but is mainly due to the bile salts it contains.

Pawlow pointed out that there is a close relationship between the amount and rate of secretion of the bile and pancreatic juice, as he showed by the diagrams reproduced in Fig. 52. He also states that the amount of fat-splitting ferment in the pancreatic secretion is dependent upon the quantity of fat in the food, basing his conclusion on experiments carried out by Walther. This observer found that in the first two hours after a meal of milk, a juice is furnished which is uncommonly rich in fat-splitting ferment, but that if the milk is deprived of its fat by filtration the juice presents a very low fat-splitting power, without any other alteration in the progress, or rate, of secretion; on again mixing the fat with the milk-filtrate, the fat ferment in the pancreatic juice is again increased to the previous amount.

Recent advances in our knowledge of the influences governing pancreatic secretion make it doubtful whether such an adaptation of the enzymes to the quality of the

food as Pawlow and others have described does occur. In this connection, the investigations that have been carried out on the presence in the pancreatic secretion of a ferment which is said to convert lactose into galactose and dextrose are of interest. Weinland, working at this subject, found that a chloroform-water extract of the pancreas of dogs fed on a diet free from milk did not affect lactose, but that a similar extract made from the pancreas of animals which had been fed on milk for several days possessed the power of converting as much

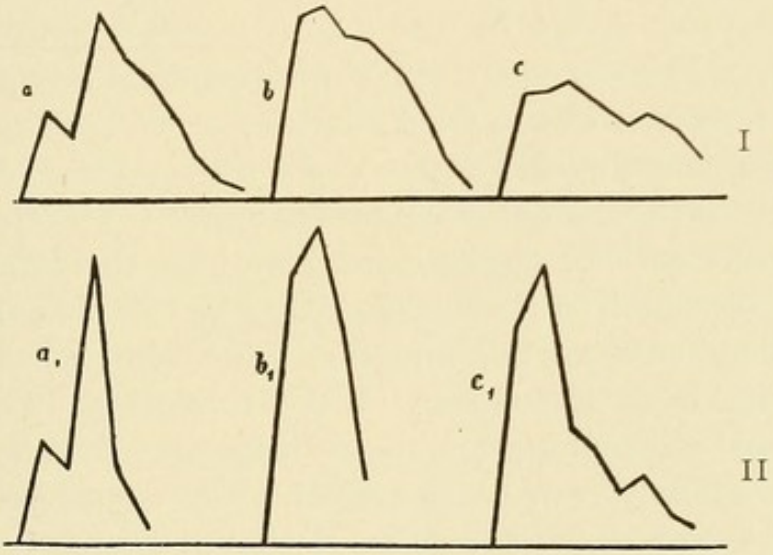

Fig. 52.—Curves representing the hourly secretion of I, Pancreatic secretion; II, entry of bile into the intestine: *a*, *a*, After ingestion of milk; *b*, *b*, after ingestion of flesh; *c*, *c*, after ingestion of bread (Pawlow).

as 50 per cent. of the added milk-sugar. He also found that the pancreas of dogs fed on meat with the addition of milk-sugar contained lactose, but that the subcutaneous injection of lactose for several days in succession had no effect in producing the ferment. He consequently came to the conclusion that the formation of "lactase" was not dependent upon any direct chemical action exerted by the lactose or its products upon the pancreas, but that the adaptation of the organ to a milk-sugar diet was brought about by a nervous mechanism.

After the discovery of secretin Bainbridge re-investigated this question, and agreed with Weinland that dogs fed on biscuits did not secrete a lactose-splitting ferment in their pancreatic juice, whereas those that were fed on milk secreted it in every instance. Extracts of the mucous membrane of milk-fed dogs injected into biscuit-fed dogs were found by him to induce the appearance of lactase in the pancreatic secretion of the latter, so that the formation of the special ferment by the pancreas appeared to depend upon some substance produced in the intestinal wall in response to the milk diet. That this was not secretin was shown by the negative result obtained on injecting secretin prepared from the duodenal mucous membrane of milk-fed dogs into biscuit-fed dogs, and the positive reaction induced by the injection of secretin from the latter into animals previously fed on a milk diet. He finally arrived at the conclusion that the adaptation of the pancreas to a diet containing lactose was brought about by a chemical, and not a nervous, mechanism resulting from the action of the milk-sugar upon the intestinal mucous membrane, and, further, that the reaction was only slowly produced. He considered that secretin evokes the secretion of all the ferment present in the pancreas at the time it is injected, and that the composition of the juice as regards its ferments for any given meal depended mainly on the previous diet of the animal, and little, if at all, upon the composition of the particular meal, excepting in so far as the nature of the food determined the amount of hydrochloric acid secreted by the stomach.

These conclusions with regard to the adaptation of the pancreas to the presence of lactose in the food have been adversely criticised by Bierry and Plimmer, who attribute the results obtained to faulty methods. Their criticism appears to be well founded and is supported by a considerable amount of careful experimental work. They agree

with Popeliski that the composition and amount of the pancreatic secretion are determined solely by the intensity and duration of the stimulus. Plimmer also points out that the work of Vasilieff and Walther, on which Pawlow based his inferences concerning the lipase and trypsin, was carried out before the discovery of enterokinase, so that its value is seriously diminished. It may therefore be concluded that, at present, there is no evidence of any adaptation of the pancreatic secretion of the diet, the only factor that influences it probably being the amount of secretin formed and the duration of its flow into the blood.

The **milk-curdling ferment** of the pancreatic juice is probably not of much physiological importance. In its general action it resembles renin, but the results produced by the two ferments are not exactly alike. Kühne was the first to demonstrate that an extract made from the pancreas of the dog produced clotting in milk, but Gamgee pointed out that this does not prove that the secretion of the organ possesses the same property. Halliburton and Brodie found, however, that pancreatic juice does produce a change in the caseinogen of milk, although the action differs from that of rennet in some particulars. They showed that the addition of pancreatic juice to milk at a temperature of 35° to 40° C. caused a finely granular precipitate of casein to form, but that the milk still remained fluid. On being cooled, however, it formed a coherent curd, which again broke up into fine granules when the temperature was raised. By the action of rennet this "pancreatic casein" can be transformed into true casein. Wohlgemuth, experimenting with the secretion from a pancreatic fistula, states that the rennetic ferment is mainly present in the form of a pro-ferment which is actuated by the intestinal juice and hydrochloric acid.

From being considered as merely an organ accessory

to the digestive tract, the pancreas has come, in recent years, to be regarded as having a most important influence upon the metabolism of the body. Not only may disease of the pancreas lead to wasting from imperfect digestion and absorption of food, but, in certain cases, it gives rise to glycosuria and other symptoms of diabetes, which suggest that it is of fundamental importance in the assimilation of carbohydrate materials by the tissues of the body. The mechanism of this influence is as yet a matter for surmise, but it is now generally assumed that, in addition to its external secretion of digestive ferments into the alimentary canal, the pancreas forms an internal secretion through which it controls carbohydrate metabolism. The elaboration of this internal secretion has been attributed by some to the islands of Langerhans, but as the discussion of this subject is intimately bound up with the relationship of the pancreas to diabetes, it will be considered later, under that heading.

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CHAPTER VIII

PATHOLOGY

Our present knowledge of the nature and etiology of the diseases to which the pancreas is liable has resulted mainly from clinical observation and experimental research upon the lower animals. Relying upon the naked-eye appearance of the organ as seen on the post-mortem table, it has been assumed, until recently, that pancreatic lesions were among the curiosities of medicine, and were therefore of little or no practical importance. Since 1889, when Fitz published his work upon acute pancreatitis and von Mering and Minkowski first brought forward the results of their investigations upon the relation of the pancreas to diabetes, it has been slowly recognised, however, that diseases of the pancreas are far from being uncommon, and that disturbances of its functions, besides interfering with the normal processes of digestion, may be responsible for signs and symptoms which had hitherto been unexplained or were usually referred to other causes.

Hale White, searching the post-mortem records of Guy's Hospital for fourteen years, 1884 to 1897 inclusive, found that in the 6708 post-mortems performed during that period the pancreas had been regarded by the morbid anatomists in charge as diseased or injured in 142 instances; that is, in 2 per cent. of all cases dying in a large general hospital. In 55 there was primary or secondary malignant disease of the pancreas; a cirrhotic hard or small atrophied gland was found in 45, and there were noticeable fatty changes in 9. Three of the remaining 33 were instances of hæmorrhage into the pancreas,

3 were cases of pancreatic calculi, 2 were examples of pancreatic cysts, 1 was a hydatid cyst of the pancreas, in 3 there was suppuration of the gland, and 4 showed evidence of tuberculosis, while the balance was made up of a miscellaneous collection of more or less rare diseases and injuries presenting obvious lesions. Recent statistics based upon microscopical investigations have shown that in many instances the gross appearance of the organ is unchanged in the presence of considerable alterations in its minute anatomy, and that acute and chronic inflammations may bring about only slight and easily overlooked microscopical changes. Bosanquet found on examining sections of the pancreas from 170 cases dying in hospital from a variety of diseases, and ranging in age from four days to over ninety years, that a certain amount of fibrosis was present in 13 per cent.; allowing, as he suggests, that some increase of fibrous tissue is the usual accompaniment of old age and that 10 per cent. of his cases, who were over forty years of age, may be excluded on that score, there still remained 5 per cent. under that age in which the microscope revealed a fibrosis, probably of pathological origin, as compared with the 0.7 per cent. recognised by the morbid anatomists at Guy's Hospital as showing evidence of chronic inflammatory changes. It is evident, therefore, that post-mortem records cannot be relied upon either for precise information as to the relative frequency of diseases of the pancreas or for data on which to base an accurate estimate of the true importance of the various morbid conditions to which it is liable, unless the results of naked-eye observations have been checked by microscopical examinations, and, since this is so rarely done even at the present time, there is not a sufficient mass of systematic observations to allow of any satisfactory conclusions being reached upon these points, apart from clinical evidence.

The difficulties met with in the recognition of morbid

conditions of the pancreas in the post-mortem room are in part due to the rapid changes that take place in the organ at and after death, and to the appearance and colour of the gland as seen at autopsy. Apart from the putrefactive changes which rapidly supervene under suitable conditions, the pancreas is said by Chiari to be more or less altered by a process of auto-digestion that sets in immediately before, or shortly after, death in some 50 per cent. of cases. In this condition the organ is white and flaccid and, under the microscope, is found to stain uniformly with acid dyes. These difficulties are to a large extent obviated in experimental researches upon animals and in observations made on man in the course of abdominal operations. Experiments upon animals can be conducted under the most favourable circumstances, and give at least some indication of what may be expected in the human subject under similar conditions, while the surgeon has the advantage over the pathologist that he can examine and handle a living organ unaffected by self-digestion and post-mortem changes, although his investigations must naturally suffer from not being as searching and conclusive as the pathologist is able to carry out. Only those who have seen and handled an inflamed pancreas can realise how an engorgement and swelling of the gland which was perfectly evident at the time of operation may, if the organ is examined a few hours later, on the post-mortem table, have entirely disappeared, leaving a structure that is pale and flaccid, presenting, in fact, no marked deviation from the normal.

The pathological conditions met with in the pancreas resemble in many respects those encountered in the liver, and in some instances a similar morbid state is found in both organs. Their parenchyma is liable to be affected by the same degenerative changes, and chronic inflammation in the one gives rise to results very similar to those induced in the other. The ducts of both organs are not

uncommonly involved in the same pathological processes, and the morbid influences reaching the one are also liable to affect the other. There are, however, certain affections of the pancreas to which no strictly analogous condition can be found in the liver, and it is to these that attention has been largely devoted in most text-books of medicine and pathology. In view, however, of the important part that the pancreas takes in the processes of digestion and internal metabolism, the neglected lesions, that are often masked by the more obvious and striking affections of other organs, are no less worthy of attention, for, although at first sight the pancreas may appear to play but a subsidiary part in the production of the symptoms met with in some of these conditions, it becomes increasingly plain, as our methods of investigation are improved, that the pancreatic lesions are responsible for much that has hitherto been attributed to disease of other organs, or been altogether unexplained.

Atrophy.—In common with other organs of the body, the pancreas is liable to diminish in size and weight with advancing years, and as the result of chronic diseases and marasmus its bulk may be reduced considerably below the normal standard. Senile atrophy of the gland is found, in many instances, to be accompanied by sclerotic changes in the vessels supplying it with blood, while in others it is no doubt the consequence of general malnutrition, such as also gives rise to the condition in chronic wasting diseases. Atrophy of the pancreas is met with in a considerable number of cases of diabetes. According to Hansemann, diabetic and cachectic atrophy can be distinguished both macroscopically and microscopically, and while the former always gives rise to diabetes, the latter only does so in advanced cases.

The pancreas in diabetic atrophy is said to be usually flabby and somewhat dark in colour. Its bulk is especially diminished in a transverse diameter, so that it

assumes a flat shape. The lobules are small, and the surrounding connective tissue and fat extend into the organ so that it is often only removed with difficulty. At times large adhesions and new-formed bands connect the pancreas with surrounding structures. Microscopically the secreting cells show no particular change, apart from the atrophy; there is no marked opacity, fatty degeneration, or pigmentation. The stroma is scanty, but the gaps caused by the diminution in size of the gland lobules are more or less obliterated. Although the organ is largely fibrous, there are here and there patches of recent cellular infiltration, giving rise to a condition resembling that met with in certain forms of granular atrophy of the kidney.

Fig. 53.—Atrophy of the pancreas (Univ. Coll. Hosp. Museum, 3194 A).

In cachectic atrophy, on the other hand, the adjacent fat tissue has disappeared to a degree corresponding to the general emaciation, and the gland is sharply defined from the surrounding structures. In shape it is cylindrical, its thickness and its height being about equal. It is not flabby, but of a firm or moderate consistency. Under the microscope both the lobules and the individual cells are small, the stroma is atrophied and scanty, and the cells are not especially pigmented.

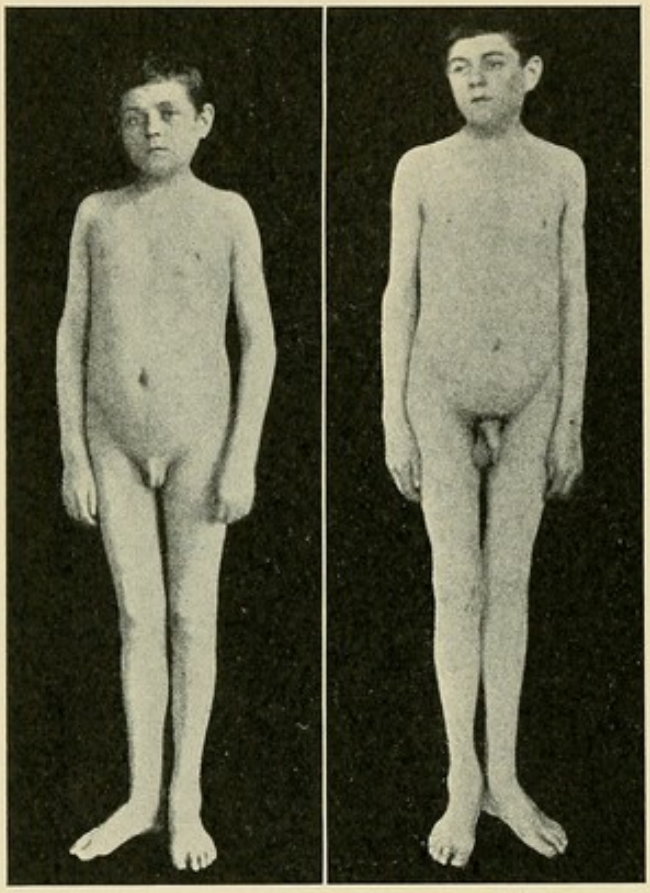
Although these observations of Hansemann's summarise the points by which cachectic atrophy may be distinguished from other conditions in which diabetes is accompanied by changes in the size of the gland, it has not been shown that his "diabetic atrophy" is a pathological entity,

or that the condition he describes under that name is invariably accompanied by diabetes; in fact, it is probable, as we shall show later, that there is no special form of diabetic atrophy, but that atrophy of the pancreas arising from a variety of causes may be accompanied by glycosuria. One of the commonest causes both of pancreatic atrophy and of diabetes is chronic interstitial pancreas, and it is to this probably that the so-called atrophy of diabetes, described by Hansemann, is in most instances due.

Williamson, Opie, and others have described cases of diabetes in which the pancreas was diminished n size to an extent bearing no relation to the wasting of other organs, although no changes could be observed in the structure of the gland. Opie suggests that in these instances the condition is possibly congenital, and that, since the pancreas is unusually small, it fails to meet the demands upon it at some period of life, so that diabetes results. He considers that when the weight of the pancreas falls below 65 grams (2 ounces) it is abnormal.

A condition apparently due to congenital deficiency of the pancreatic functions has been described by Byrom Bramwell under the name of "pancreatic infantilism." The patient in whom this diagnosis was made was a youth of nineteen whose bodily development had apparently been arrested about the age of eleven years. He was bright and intelligent, perfectly formed, and presented none of the physical alterations suggestive of sporadic cretinism. The abdomen was swollen and tympanitic, and for nine years before he came under observation he had suffered from chronic diarrhœa. The urine was free from sugar. From careful investigations of the urine and fæces it was concluded that the pancreatic secretion was defective or completely absent. That this was the case was proved by the remarkable improvement brought about by the administration of a glycerine extract of pancreas, for as the result of this treatment the stools

were reduced from five or six loose motions a day to two, one of which was formed; in two years he grew five inches, and increased 1 stone 8 pounds in weight, although for the previous eight years he was said not to have grown at all; the sexual development, which before treatment was begun was infantile, progressed in a normal manner; the patient looked much older, and his voice, which had previously been high-pitched and childish, became of low tone and rough.



a *b*

Fig. 54.—Pancreatic infantilism: *a*, Before treatment; *b*, after treatment (Byrom Bramwell).

Thomson has since described two apparently similar cases in males and Rentoul has recorded the case of a female with similar symptoms. The first of Thomson's cases was a man of twenty-four who was about the size of a boy of ten; the second was a boy of eighteen who resembled a child of eight or nine years in size and development; both suffered from chronic intractable diarrhœa. In Rentoul's case the patient was a girl of eighteen whose parents complained that for seven years she had not grown, and that she had been troubled all her life with diarrhœa. This patient was

also much benefited by pancreatic extract, putting on 9½ pounds in weight and adding almost 2 inches to her height in a little over four months, besides developing sexually and improving in her general condition.

Whether pancreatic infantilism is due to congenital atrophy of the pancreas or, as has been suggested, to general fibrosis from congenital syphilis, it would appear that while in patients who present such symptoms the pancreas is sufficient for the metabolic needs of the body for the first eight or nine years of life, it is subsequently unable to keep pace with the calls upon it, so that the general nutrition and development suffer in consequence. It is worthy of note, however, that the deficiency appears to be confined to the digestive functions of the gland and does not interfere with carbohydrate metabolism, for none of the recorded cases have had glycosuria. Whether diabetes will subsequently develop or not it is as yet too early to say, but the history of a case in this connection would be well worth following up as growth advanced.

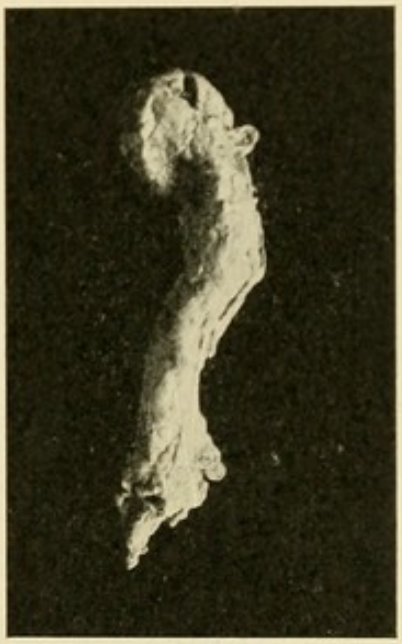


Fig. 55.—Fibrosis of the pancreas (St. George's Hospital Museum).

As the result of pressure exerted from without by aneurysms, new-growths, etc., the pancreas may undergo secondary atrophic changes, and similar consequences may also follow the chronic interstitial inflammation accompanying pancreatic calculi, pancreatic cysts, hæmorrhage, or abscess formation. In some instances the changes may be so great that the gland tissue almost

entirely disappears and the organ is only represented by a small mass of fibrous tissue.

Fatty Infiltration and Degeneration.—The interstitial connective tissue of the pancreas normally contains a certain amount of fat, and this is liable to increase under pathological conditions. The increase that takes place in simple cachectic atrophy has already been re-

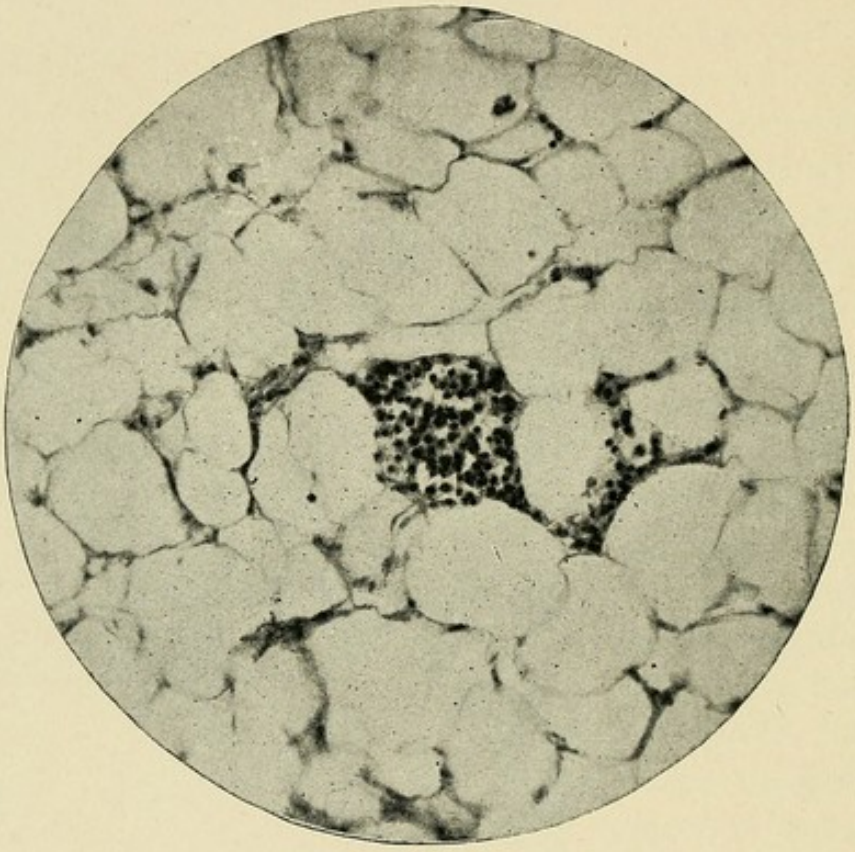


Fig. 56.—Chronic atrophic pancreatitis. Island of Langerhans, surrounded by fat, instead of acini (Deaver and Müller).

ferred to. In general obesity, especially when connected with alcoholism, a similar overgrowth of fat is frequently encountered. This condition is often combined with fatty degeneration, and, in extreme cases, may result in the whole organ being transformed into a mass of fatty tissue. It is then of a yellow or yellowish-white appearance, soft, and somewhat larger than normal.

On section it is found to be lobulated and to consist of masses of fat separated by more or less well-marked strands of fibrous tissue in which the remains of the larger ducts, and perhaps some remnants of the gland structures, are embedded. Fatty degeneration is caused most frequently by inflammation of the gland, but it also occurs in infectious diseases and toxæmias, and may result from poisoning by phosphorus or mineral salts. Extreme degrees of fatty change are frequently found associated with pancreatic lithiasis. Fatty degeneration of the parenchyma is preceded in the first instance by cloudy swelling, the cells microscopically being found to be somewhat enlarged, opaque, and very granular. To the naked-eye the gland is hyperæmic and enlarged. At first it is hard to the touch, but, as the degenerative process advances, becomes softer and of a white or yellowish-white colour. Under the microscope the epithelium is then found to contain numerous fat globules and the interstitial tissue to be œdematous.

Amyloid degeneration of the pancreas occurs under the same conditions as in other organs, and is associated with a similar lesion in other tissues of the body. It primarily affects the small blood-vessels, but may eventually involve the larger vessels and the membrana propria of the acini. The gland cells undergo fatty degeneration and, in part, disintegrate. Hennigs found, in one hundred and fifty-five cases of general amyloid disease, six in which the pancreas was affected. Rokitansky states that sometimes the degenerative changes are limited to the pancreas and may affect the secreting epithelium, but this is denied by Friedrich and Kyber. Opie suggests that the condition observed by Rokitansky in these cases was in reality hyaline degeneration.

Hyaline degeneration of the parenchyma of the pancreas has been described by Saunby in a case of diabetes, and Opie has also published an account of a diabetic whose pan-

creas showed patches of hyaline degeneration, apparently replacing the islands of Langerhans, but also affecting the secreting parenchyma. Other cases of hyaline degeneration have since been recorded by a number of investigators. All have been associated with diabetes and the degenerative changes have been said to have been limited to the islands of Langerhans. According to Opie, hyaline de-

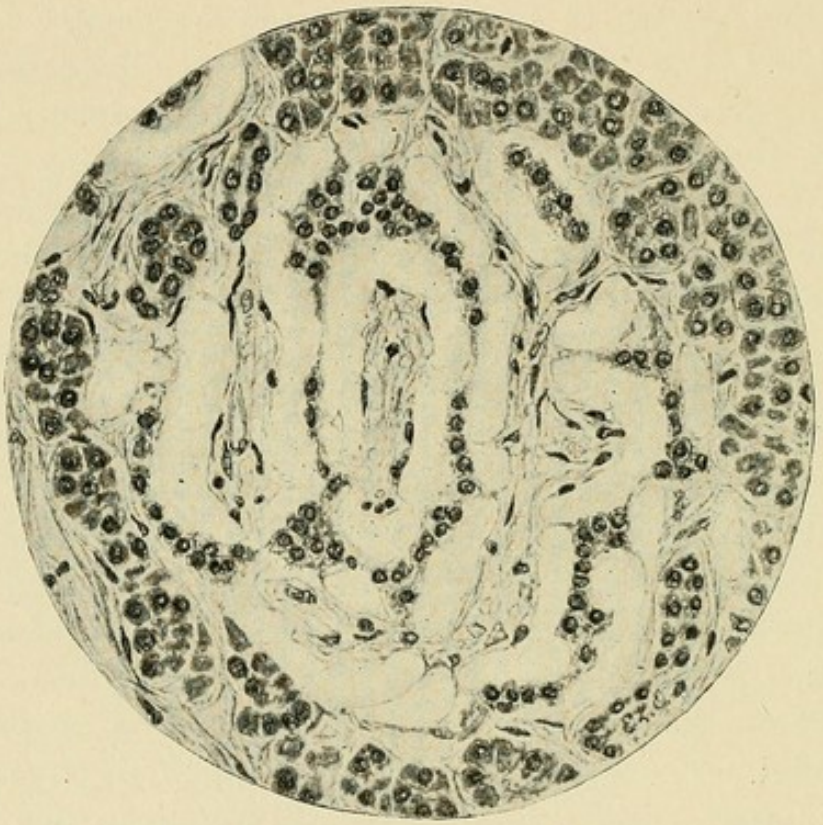


Fig. 57.—Hyaline degeneration of the pancreas (Opie).

generation first manifests itself by an increase in the size of the cells of the islets and an alteration of their protoplasm. With the death of the cells their nuclei disappear, and the cell protoplasm, which stains with acid dyes, remains for a time granular, but subsequently becomes homogeneous. The small masses of hyaline material then fuse with one another and form large collections which lie in contact with the fibrous septa of the

island. After complete transformation of its cells the island is found to be represented by a hyaline mass, penetrated by the remains of altered capillaries. In some instances the degenerative process may spread to the secreting parenchyma, but, as a rule, it is limited to the cell islets. The hyaline material stains with eosin, picric acid, and other acid dyes, but shows no affinity for nuclear stains; on treatment with iodine, gentian-violet, methyl-violet, or iodine-green it does not give the amyloid reactions, and it resists the action of strong acids and alkalies. Unlike amyloid changes, hyaline degeneration of the pancreas is limited to that organ, for the blood-vessels of the liver, spleen, and kidneys appear to be unaffected. Its etiology is uncertain, but the fact that, in most cases, there has also been chronic interstitial pancreatitis of the interacinar type has suggested that it may possibly be due to interference with the circulation in the cell islets. Opie, however, is of opinion that both lesions are due to some irritant carried to the pancreas by the blood.

Focal Necrosis.—In the body of a male negro, who had suffered from diabetes, Opie met with a condition of the pancreas resembling the focal coagulation necrosis frequently observed in the liver in typhoid fever and other infections. To the naked eye the organ presented no notable abnormality, but microscopically there was some increase of the connective tissue, and foci of necrosis, involving a considerable number of acini, were found in the parenchyma. In some places the islands of Langerhans were found to be implicated in the process, and, rarely, the cells of an island had undergone necrosis while the surrounding acini were normal. The affected cells preserved their identity and were not fused into homogeneous masses, as in hyaline degeneration, but they had lost their nuclei and stained deeply with eosin.

Local hæmorrhages into the tissues of the pancreas are

relatively frequent. In some instances they are associated with extravasations of blood in other organs and result from circulatory disturbances, due to diseases of the heart, lungs, and liver, or from altered conditions of the blood, such as occur in infectious diseases, purpura, scurvy, phosphorus-poisoning, etc. Diseases of the blood-vessels, such as atheroma, and fatty degeneration, or alcoholic or syphilitic arteritis, may also be associated with hæmorrhage into the gland. Among other causes of pancreatic hæmorrhage may be mentioned fatty degeneration of the gland cells, with a deposit of fat in the pancreas, the result of alcoholism or of general obesity, fat necrosis in the gland or its vicinity, disintegration of neoplasms, embolism of a pancreatic artery, and inflammations of the gland, which last will be considered in detail subsequently. Although the pancreas lies in a sheltered position within the abdominal cavity, its tissues are comparatively soft and easily bruised, so that even slight injury takes more effect upon it than upon firmer organs, and may give rise to an effusion of blood. This susceptibility of the pancreas to injury is shown by the effects of manipulations of the gland in animals, and must be borne in mind in conducting operations for gall-stones in the common duct, for it is then often necessary to manipulate the head of the pancreas rather freely. Large pancreatic hæmorrhages are of great clinical interest and are probably more common than is usually thought. They may occur in the substance of the gland and disintegrate it, or on the surface and lead to extensive effusion, either beneath the peritoneum or into the lesser sac.

Besides the local hæmorrhages not associated with inflammatory change, which may be termed "pancreatic apoplexy," and the form accompanying acute inflammation, known as "hæmorrhagic pancreatitis," there is, in many pancreatic affections, a tendency to general hæmor-

rhage from wounds or mucous surfaces, and to petechial hæmorrhage into the skin, or to more extensive bleeding into the subcutaneous tissue. It is well recognized that a hæmorrhagic tendency coexists with cancer of the head of the pancreas, and it is generally thought to be alto-

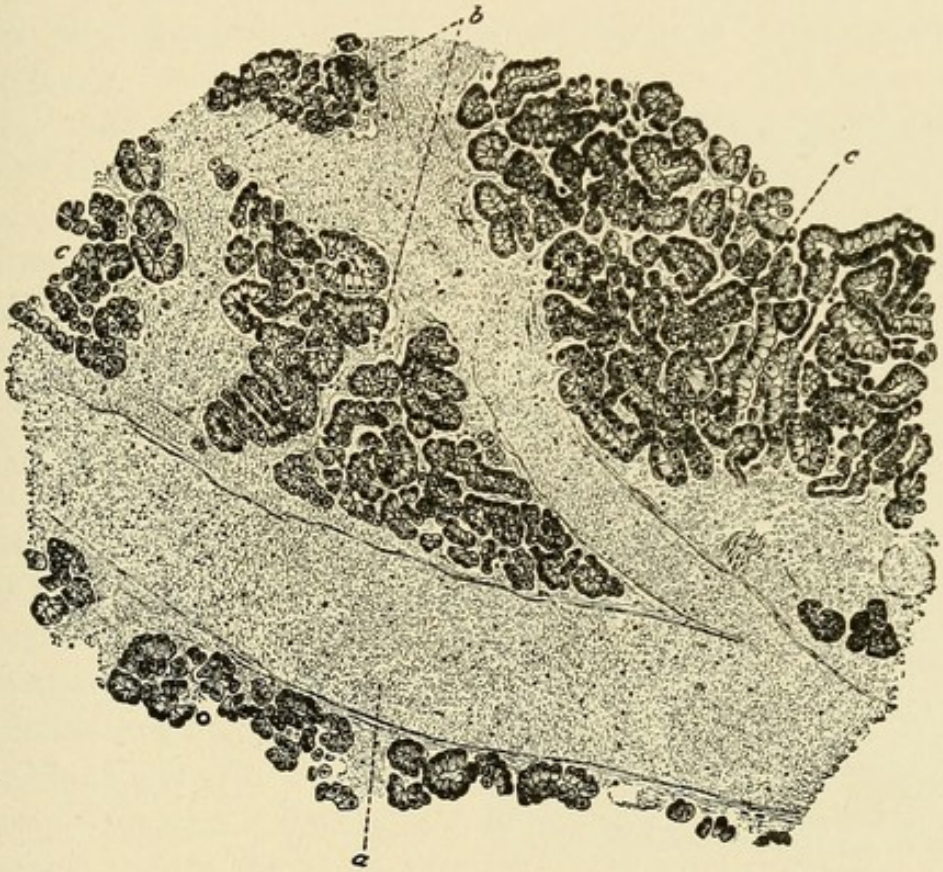


Fig. 58.—Hæmorrhage into the pancreas produced by the injection of zinc chloride, showing how the blood infiltrates and breaks up the gland tissue: *a*, Blood-vessel distended with blood; *b*, extravasated blood in the parenchyma between the lobules; *c*, normal pancreatic tissue (Oser).

gether dependent upon the attendant cholæmia. There is, however, much less danger from hæmorrhage in patients jaundiced from gall-stones than in those in whom the jaundice depends upon disease of the pancreas. The hæmorrhagic tendency is, moreover, also present, although perhaps not to quite the same extent, in some pancreatic affections not associated with cholæmia. Investigations

of the blood that we have carried out in a number of cases of cancer of the head of the pancreas and in inflammatory affections of the gland, with and without jaundice, have shown that the coagulation time of the blood, as estimated by Wright's method, is considerably delayed and the number of blood platelets markedly diminished. It is well known that a diminution in the lime salts of the blood interferes with its power of coagulating, and that the prolonged coagulation time and tendency to hæmorrhage in pancreatitis are probably due to a great extent to this cause is suggested by the beneficial effects resulting from the administration of calcium chloride. Further evidence, pointing in the same direction, is also afforded by the composition of pancreatic calculi, which are peculiarly rich in calcium, and by the very frequent presence of a large deposit of calcium oxalate crystals in the urine in cases of pancreatitis.

Inflammatory Affections.—Judging from post-mortem records, inflammatory affections of the pancreas must be considered as amongst the rarest of diseases, but recent clinical observations and operative experience have shown that such a conclusion would be far from being the truth. As far back as 1672, Tulpius described a diffuse pancreatic abscess of pyæmic origin, and Matthew Baillie, in a work on "Morbid Anatomy," figured what he called a hard pancreas, with the lobules distinct, but which would now be considered as an example of chronic pancreatitis. In the same work Baillie also gives a drawing of a pancreas in which concretions were discovered in the ducts post-mortem, and which shows the changes that accompany them, as well as the relations of the bile and pancreatic ducts, in a striking manner. Portal in 1804 described a case of acute suppurative pancreatitis, following an attack of gout in the feet, and Percival in 1818 recorded a well-marked case of pancreatic abscess associated with jaundice.

Acute pancreatitis with fat necrosis was first described by Balser in 1879, but it was not until 1889, when Fitz published his classical papers, that the attention of the medical world was really aroused and inflammatory diseases of the pancreas came to be carefully studied at the bedside and in the laboratory. Much experimental work has been since devoted to the investigation of acute pancreatitis, for opportunities of studying the disease clinically, although more frequent than has been supposed, are still not common. Our present knowledge of the chronic inflammatory affections of the pancreas, however, while dependent to a certain extent upon the results of experiment performed in animals, is mainly due to clinical research and observations made in the course of operations upon the biliary tract.

Fig. 59.—Acute hemorrhagic pancreatitis (Univ Coll. Hosp. Museum, 3194 B).

Experiment has shown that the injection of a variety of substances into the pancreas, either directly into the parenchyma or through the duct of Wirsung, gives rise to severe, and often rapidly fatal, inflammation, the severity of the lesion depending upon the nature and amount of the substance injected.

The most varied and successful experiments have been carried out by Flexner, who found that dilute hydrochloric, nitric, sulphuric, or chromic acid, solutions of caustic

alkalies, formalin, or suspensions of bacillus pyocyaneus or of bacillus diphtheriæ, when injected into the pancreatic duct of dogs gave rise to acute inflammation of the gland, which, in rapidly fatal cases, was commonly accompanied by hæmorrhage, fat necrosis, and glycosuria. In those instances in which the animal survived for some time necrosis of portions of the gland, abscess formation, and, occasionally, chronic interstitial inflammation were met with. Subsequently Flexner and Pearce showed that the introduction of artificial gastric juice into the duct gave rise to similar changes, but that injections of sterile blood, while they occasioned an increase of fibrous tissue, did not produce acute inflammatory changes.

Previous to these experiments by Flexner and Pearce, acute hæmorrhagic pancreatitis had been produced in dogs, by Hlava, from injections of artificial gastric juice, and he suggested that the cause of acute pancreatitis in man lay in the passage of hyperacid gastric juice into the pancreatic duct through anti-peristaltic action in the intestine. There is, however, no evidence which would lend support to such a view, and it cannot be accepted as a likely explanation.

Hlava and Carnot, as well as Flexner, have induced acute pancreatitis by injections of a variety of bacteria, or, in some instances, of their toxines, into the pancreatic duct, and, since a large number of different organisms have been isolated from the pancreas in cases of acute pancreatitis, it has been suggested that the condition is dependent upon bacterial invasion from the intestine. It is now agreed by almost all writers upon the subject that the bacteria isolated in these cases have no etiological connection with the lesion and are only present through secondary invasion of the injured tissues.

Hess has produced necrosis, with hæmorrhage and fat necrosis, by injections of olive oil into the pancreatic duct, and has advanced the hypothesis that this effect

was brought about by the products into which the oil was split by the steapsin of the pancreatic juice. To verify this he studied the effects induced by injections of fatty acids, soda-soap solutions, and glycerine into the duct. Oleic acid, and 4 per cent. soda-soap solution, were both found to produce the same result as the oil, but glycerine failed to give rise to any acute inflammatory changes. In consequence of the results obtained in these experiments Hess suggested that regurgitation of fatty substances from the intestine, favoured by widening and injury of the duodenal orifice of the common duct by the passage of a gall-stone, was a possible cause of human pancreatitis. He has also suggested that poisoning with soap might be the cause of death and of the symptoms of intoxication that precede it, for Munk and Freidenthal have shown that the injection of 0.1 gram of soap per kilo of body-weight into the vessels of an animal brings about collapse and death.

More recently Guleke has succeeded in producing acute pancreatic necrosis in 20 out of 27 dogs by ligaturing the pancreatic duct close to the duodenum, and injecting 5 per cent. of oil on the pancreatic side of the ligature. In the majority death took place six to twenty hours after the operation, but in three, where extensive necrosis was present, the fatal termination was delayed three to six days. In seven of the animals no effect was observed for seven to ten days. They then had loss of appetite, became emaciated, had fatty stools, and died seventeen to twenty-one days after the operation, excepting one strong young animal, which survived. Post-mortem the pancreas was found to present characters closely simulating those seen in man in chronic pancreatitis.

Guleke has also induced acute necrosis, terminating in death in twenty to thirty hours, by injecting oil into the arteries supplying the pancreas, thus producing artificial infarcts.

The association of diseases of the pancreas with morbid conditions of the biliary passages has been pointed out by a number of observers, and since in most individuals the common bile-duct and pancreatic duct unite to form a common channel before entering the duodenum, and, in many persons (62 per cent., Helly), the common duct is embedded in the tissue of the pancreas for a part of its course, such a connection is probable on anatomical grounds. The possibility that a gall-stone lodging in the diverticulum of Vater might produce conditions favourable to the passage of micro-organisms into the pancreas was suggested by Lancereaux, but that such an event might also bring about the penetration of bile into the pancreatic duct was first clearly demonstrated by Opie.

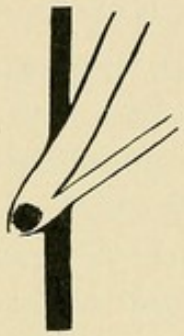


Fig. 60.

Fig. 61.

Figs. 60 and 61.—Fig. 60, Diagram to show how a small gall-stone may obstruct the papilla, and, if the ampulla of Vater be very large, may convert the common bile-duct and duct of Wirsung into one canal, thus predisposing to acute pancreatitis. Fig. 61, Diagram to show a method of termination of the ducts which will not predispose to pancreatitis (Opie).

In an autopsy on a case of acute pancreatitis under Halstead's care Opie found a small gall-stone impacted in the duodenal orifice of the ampulla of Vater, which, while too large to pass into the duodenum, was yet too small to fill the diverticulum and close the opening of the pancreatic duct. The bile and pancreatic ducts were thus converted into a continuous channel, and that the contents of the former had passed into the duct of Wirsung was shown by its walls being deeply stained with bile. Investigating the literature of the subject Opie collected thirty-nine cases of acute pancreatitis associated with gall-stones, situated either in the gall-bladder or in the bile-ducts,

and in eight of these he found that there was a calculus in the diverticulum of Vater. It appeared possible, therefore, that the entrance of bile into the pancreatic duct was the cause of the pancreatitis in a considerable proportion of cases. In attempting to verify this experimentally, Opie showed that the injection of 5 c.c. of bile into the pancreatic duct of dogs set up acute inflammatory changes, which in some instances were fatal within twenty-four hours.

While claiming that bile diverted into the pancreatic duct by a biliary calculus had thus been shown, both clinically and experimentally, to be capable of producing acute pancreatitis, Opie pointed out that it could not be demonstrated that all cases of acute pancreatitis were dependent upon this cause. Such an effect can take place only when the gall-stone is very small, and the anatomical conditions of the duodenal orifice and of the diverticulum of Vater are favourable. Measurement of the diverticulum of Vater by Opie proved that in about 30 per cent. of cases a small calculus could probably lodge in the opening of the diverticulum and yet only partially fill the cavity, and, as in one out of ten individuals the bile-duct joins the smaller pancreatic duct, while the larger duct of Santorini enters the duodenum at the site of the lesser papilla, the necessary anatomical conditions are present in but a small proportion of cases, and the rarity of acute pancreatitis from this cause, when compared with the relative frequency of cholelithiasis, is not difficult to explain. It has been shown by more than one observer that the lower end of the biliary passage in the dog is normally the habitat of pyogenic bacteria, and it has been suggested by Trevor that the experimental injection of bile, and other substances, into the pancreatic duct may produce its effect by lowering the resistance of the walls of the duct, thus allowing the entrance of septic organisms. Recent experiments by Flexner, however, tend to prove

that the inflammatory changes are directly due to the action of the bile salts upon the pancreatic cells, and it is probable that other irritating substances may act in a similar manner.

The experimental evidence already quoted has demonstrated that the injection of various substances into the pancreatic duct, or tissue of the pancreas, gives rise to

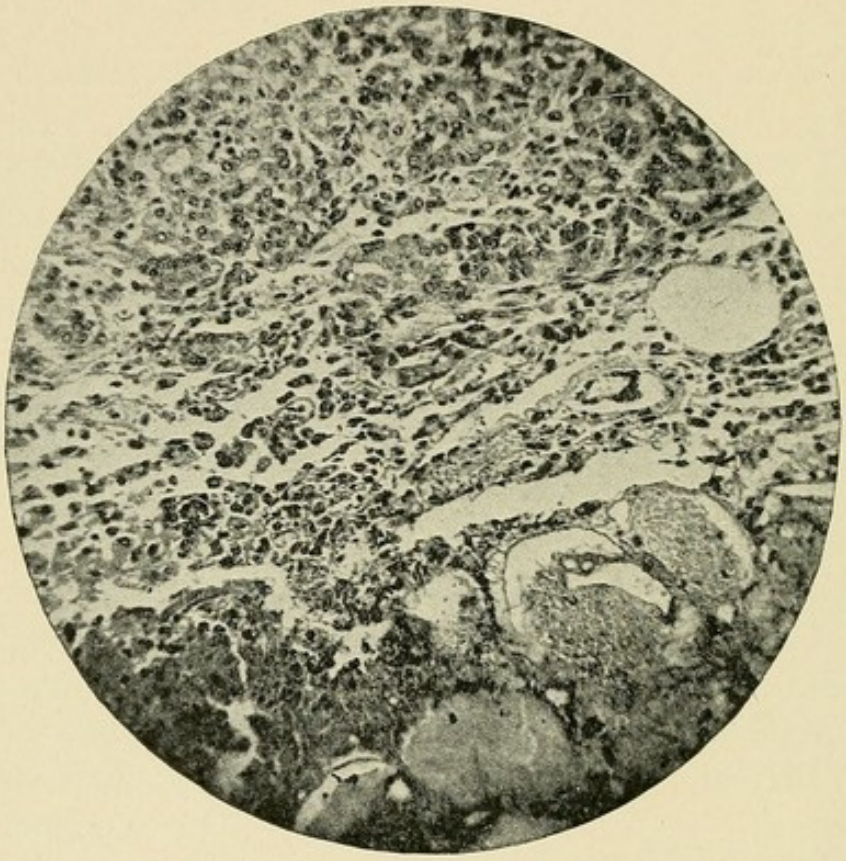


Fig. 62.—Acute hæmorrhagic necrosis (above). Zone of leucocytes and red cells, acini, swollen and cloudy (below) (Deaver and Müller).

acute changes which, in many instances, are accompanied by an effusion of blood, thus giving rise to what is clinically termed "*hæmorrhagic pancreatitis.*" In some instances, however, where the animal has survived for a more or less lengthy period we have seen that purulent changes, or necrosis of portions of the gland substance, have been found. These may be regarded as correspond-

ing to suppurative and gangrenous pancreatitis respectively as met with in man. It would therefore appear that hæmorrhagic, purulent, and gangrenous pancreatitis, in spite of the differences in their morbid appearances, are probably but phases in the same process, and that, as Opie has remarked, gangrenous pancreatitis is but a late stage of the hæmorrhagic form.

The pancreas in hæmorrhagic pancreatitis is enlarged; its interstitial tissue, as well as the tissues in its neighbourhood, is infiltrated with blood. Microscopically the parenchyma is necrotic and infiltrated with cellular

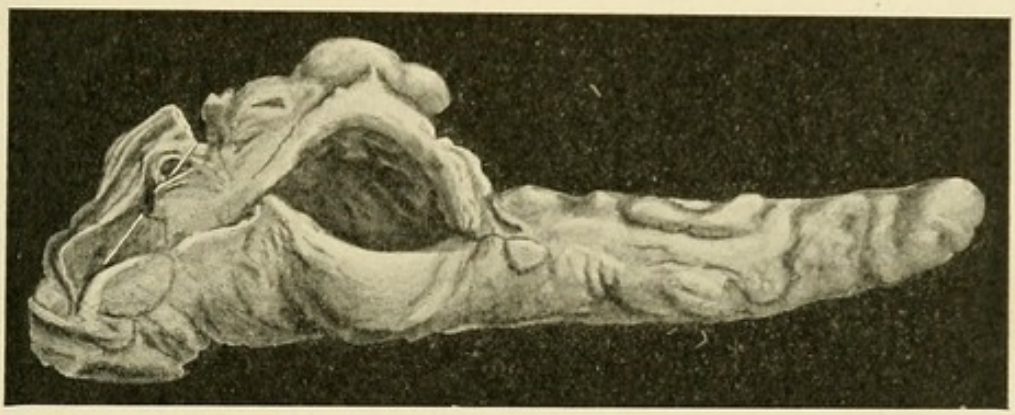


Fig. 63.—Abscess of the pancreas (Royal College of Surgeons Museum, 2832).

and fibrinous exudates. Numerous foci of disseminated fat necrosis are always found in the omentum and subperitoneal tissue.

In *suppurative pancreatitis* the gland contains one or more abscess cavities of varying size. It may be enlarged, from the accompanying inflammatory changes, and the surrounding tissue may be indurated and adherent. The history of suppurative pancreatitis is always much longer than that of the hæmorrhagic form, as the results of animal experiments would suggest, and may extend to weeks or even months.

Gangrenous pancreatitis rarely proves fatal until some

little time after the first onset of the symptoms. The organ after death is dry and dark, or even black, and is enlarged and friable. If the process extends to the surrounding tissues, and affects the lesser peritoneal sac, this may be converted into an abscess cavity containing pus and necrotic material, in which the remains of the gangrenous pancreatic tissue lie. In about half the recorded cases there has been evidence of previous hæmorrhage in the altered gland, which points to its frequently being the result of hæmorrhagic pancreatitis in man, as in animals. Disseminated fat necrosis is constantly found in gangrenous pancreatitis, but is uncommon in the suppurative form.

In the past considerable importance has been attributed to the action of trypsin in the production of necrosis and other pathological conditions in the pancreas, but, as the pancreatic secretion is now known to have but slight proteolytic powers until it has been activated by the enterokinase of the succus entericus, and there exist in the blood anti-bodies to both trypsin and enterokinase, this explanation cannot now be considered as of much weight. Trypsin poisoning, however, is considered by Guleke to be the true cause of death in acute necrosis of the pancreas. He found that if the pancreas from one dog is introduced into the abdominal cavity of another, the same clinical symptoms and intra-abdominal picture, excepting for the local condition of the dog's own pancreas, are produced as are seen in cases of acute necrosis. He also found that constitutional symptoms resembling those seen in acute necrosis were induced by intravenous, intraperitoneal, or subcutaneous injections of trypsin, but that if the animal were immunised against trypsin by gradually increasing doses, the introduction of an extirpated pancreas into the abdominal cavity was not so rapidly fatal as in unimmunised animals.

A question that has been much debated is the *rela-*

tion of pancreatic hæmorrhage to acute pancreatitis. Two possibilities present themselves: (1) that the hæmorrhage is a consequence of the inflammation; (2) that the hæmorrhage is the primary factor and the inflammatory changes secondary phenomena. Fitz, Orth, Birch-Hirschfeld, Zeigler, Körte, and most modern writers on the subject hold that the inflammation precedes the hæmorrhage, and the first named has in consequence designated the disease "hæmorrhagic pancreatitis." Dieckhoff, Seitz, and Hawkins maintain, on the other hand, that the hæmorrhage precedes the inflammation, which is, in fact, caused by a bacterial infection of the hæmorrhagic effusion. Seitz considers that in the cases recorded by Fitz and others as examples of hæmorrhagic pancreatitis, conclusive evidence in proof of their conclusions was not offered in a single instance, and he further contends that if the hæmorrhage were secondary to the inflammatory changes cases would from time to time occur in which there was a rapidly fatal inflammation without hæmorrhage. Cayley has since reported a case, presenting symptoms of acute pancreatitis, which was fatal on the fourth day, and on post-mortem examination the pancreas was said to show evidence of acute inflammatory changes. There was neither hæmorrhage nor suppuration in the gland, but a general infiltration with blood-coloured serum in and around it. From this case Cayley argues that hæmorrhage is not an essential feature of acute pancreatitis. A similar case which proved fatal forty-eight hours after the first onset of the symptoms has also been recorded by Kennan. The pancreas in his case was markedly enlarged from inflammatory changes, the common bile-duct and the gall-bladder contained numerous gall-stones, and a calculus the size of a pea was found in the duodenum.

A study of the reported cases of "hæmorrhagic pancreatitis," and of those we have had the opportunity of

ourselves observing, suggests that both views may be correct in different cases, for although a primary pancreatitis may be accompanied by hæmorrhage, this origin is not the only one, and there are many cases in which hæmorrhage precedes and, in fact, is a cause of inflammation. This is due, first, to the great tendency of the gland to disruption, because of its soft structure, when hæmorrhage does occur; secondly, to the communication of the gland with the intestine, which renders the access of putrefactive organisms likely; thirdly, to the great tendency of the damaged gland and effusion to decompose as soon as organisms gain access to them. This view of the subject has at least the merit of simplicity, and br ngs "hæmorrhagic" pancreatitis into line with other well-known inflammations.

Suppurative pancreatitis and abscess of the pancreas are sometimes met with as the result of extension from neighbouring organs, and more particularly from the stomach. Dieckhoff has reported a case of secondary suppuration associated with cancer of the duodenum, and Hale White speaks of an instance of abscess of the head of the gland in a patient who died of a malignant growth of the sigmoid flexure.

Pyæmic abscesses of the pancreas are rare, but have been met with in cases of pyæmia and puerperal fever. Lancereaux refers to a case of abscess of the pancreas due to the pneumococcus.

The injection of foreign substances into the parenchyma and ducts of the pancreas in some instances, instead of giving rise to the acute changes already described, causes local or general *induration of the gland*, accompanied by an overgrowth of the interstitial tissue. Körte found that injections of oil of turpentine caused very intense interstitial changes, and Oser showed that indurative pancreatitis followed the injection of alcohol and zymine into the parenchyma. Flexner produced sclerosis by

injecting 3 per cent. agar into the pancreatic ducts, and in seven out of twenty-seven dogs, Guleke, as we have seen, induced chronic pancreatitis by injecting oil into the ligatured pancreatic duct. Two animals were also injected by the last-named observer with blood drawn from the femoral vein; both showed signs of pancreatitis; one recovered, but the other died of chronic pancreatitis in three weeks. Körte and Senn produced indurative pancreatitis by injury of the pancreas, and Sandmeyer has found that sclerotic changes take place in the portions of pancreatic tissue left after partial extirpation. Evidences of chronic inflammatory changes also develop early, according to Flexner, around acute lesions in dogs. The overgrowth of connective tissue caused by oil of turpentine is said by Körte to be increased by crushing, tearing, or cutting the gland.

The part played by micro-organisms in the production of chronic pancreatitis has been investigated by Körte and Carnot. The former demonstrated that injections of pure cultures of bacillus coli caused more or less extensive interstitial changes, and that fæcal matter gave rise to similar results. Carnot, by an ingenious device, produced sclerosis of the pancreas from an ascending infection from the duodenum. A thread was fixed in the pancreatic duct and carried through its orifice into the duodenum, where it was allowed to hang free, and, when the animal was subsequently killed, the walls of the duct were found to be infiltrated with leucocytes and thickened, while there was a well-marked overgrowth of the interstitial tissue in the gland parenchyma.

The ascending infection from the duodenum thus demonstrated by Carnot as a possible cause of chronic pancreatitis is no doubt operative in man under certain circumstances, since a history of dyspepsia and intestinal derangement, with or without vomiting, is not uncommon in this disease. The changes in the pancreatic functions

thus brought about are probably responsible for the continuance of many cases of chronic dyspepsia in which the relation is not usually recognized, for, while the changes in the pancreas may be initiated by pathological conditions in the intestine, the diseased pancreas, not being capable of properly performing its functions, will accentuate and prolong any digestive disturbances that may be present.

The entrance of micro-organisms into the duct of Wirsung is normally prevented by the flow of the secretion and the valve-like folds in the walls of the diverticulum of Vater, but the duct of Santorini is not thus protected, for, according to Desjardins, the secretion may there flow indifferently towards the intestine or from the intestine towards the gland. Organisms carried in from the duodenum by a reverse current will be conveyed through the substance of the organ to the point where the ducts of Santorini and Wirsung are connected, and there, meeting with the direct current in the main duct, will be carried into the intestine again. These circumstances would naturally favour the infection of the gland, and particularly the head, when from any cause the virulence of the intestinal organisms is increased, or the resistance of the pancreatic tissue is lowered. The area of the pancreas enclosed between the duodenum to the right, the duct of Santorini above, and the duct of Wirsung below, has been termed the "triangle of infection of the pancreas," and represents the most frequent site of inflammatory changes in the gland.

Chronic pancreatitis is produced experimentally with the greatest degree of certainty, and is found most commonly in man, as a consequence of obstruction of the ducts. Pawlow has produced interstitial pancreatitis in rabbits by ligature of the pancreatic duct; Langendorff has obtained similar results in pigeons; Schulze, working with guinea-pigs, Ssobolew with rabbits, dogs, and cats,

Opie and other observers with cats and dogs, have also produced an overgrowth of connective tissue in the pancreas by a similar method. The pathogenesis of the condition is not, however, quite clear. Carnot has suggested that the retained secretion has a toxic effect upon the parenchyma of the gland, and, since the obstruction of the flow will favour the entrance of micro-organisms from the duodenum, chronic inflammatory changes are set up which result in disappearance of the secreting cells and an increase of the interstitial connective tissue. He has also suggested that the reflex nervous stimuli which were believed to give rise to the pancreatic secretion were no longer able to excite normal functional activity when the ducts were obstructed, so that the cells might atrophy as muscle fibres do after section of their motor nerve. The discovery of secretin, while it has deprived this hypothesis of the basis on which it was founded, has not altogether disposed of it, for it is conceivable that the constant stimulation of the cells by secretin may eventually give rise to atrophy when they are working against a pressure that they cannot overcome, in a similar manner to that in which the kidney undergoes changes in obstruction of the ureter.

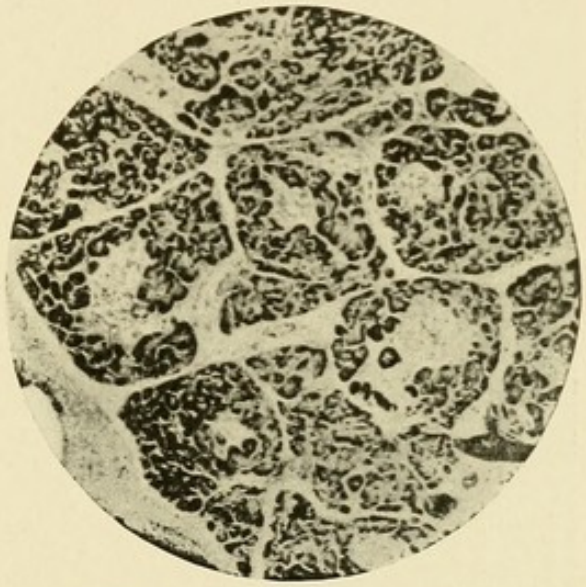


Fig. 64.—Chronic interstitial pancreatitis in a cat following ligation of the pancreatic ducts (Opie).

Clinical observation has shown that, although chronic pancreatitis may arise from obstruction of the duct due

to the pressure of tumours, stenosis of the duodenal orifice following ulceration, growth in the duodenal papilla or ampulla of Vater, and the presence of impacted pancreatic calculi, intestinal worms, or portions of hydatid membrane in the duct, it is most commonly associated with cholelithiasis. The great practical importance of the association, and the frequency with which inflammatory enlargement of the head of the gland accompanies gall-stone trouble, were first brought to the notice of the profession in a lecture delivered by one of us at the London Polyclinic in July, 1900, and it was then shown that surgical treatment is capable of affording complete relief in nearly all cases. It has since been pointed out that Riedel had published, in 1896, an account of three cases in which he drew attention to the relation of chronic pancreatitis to cholelithiasis, but we were unacquainted with his work at the time this lecture was given, and his observations do not appear to have attracted notice until after that date. The first case of chronic pancreatitis actually operated on was by one of us in June, 1890, the patient being alive and well in 1905. In this instance the pancreas was enlarged and hard, and malignant

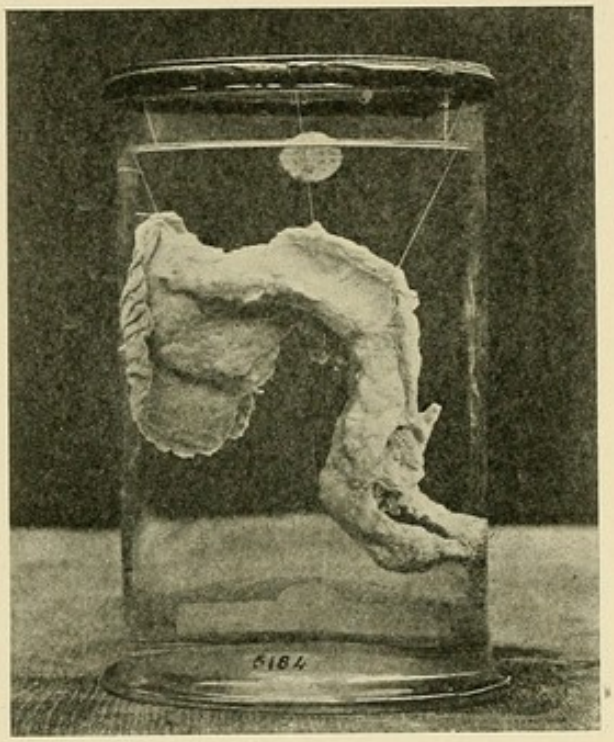


Fig. 65.—Cancer of the duodenal papilla, with dilatation of duct of Wirsung and chronic pancreatitis (St. George's Hosp. Museum, 113 K).

disease was, at the time, suspected, but her ultimate complete recovery suggested the true explanation. In April, 1892, however, a case was operated on in which the condition was proved by microscopical examination, and this, which was investigated a year before Riedel's first case, in 1893, is, so far as we can find, the earliest instance where chronic pancreatitis was conclusively demonstrated. A large number of cases are now on record in which various surgeons have observed induration of the head of the pancreas associated with gall-stones. The published cases cannot, however, be taken as truly representing the frequency of the condition, for, in our experience, pancreatitis is met with in about 60 per cent. of cases in which gall-stones are found in the common bile-duct at operation.

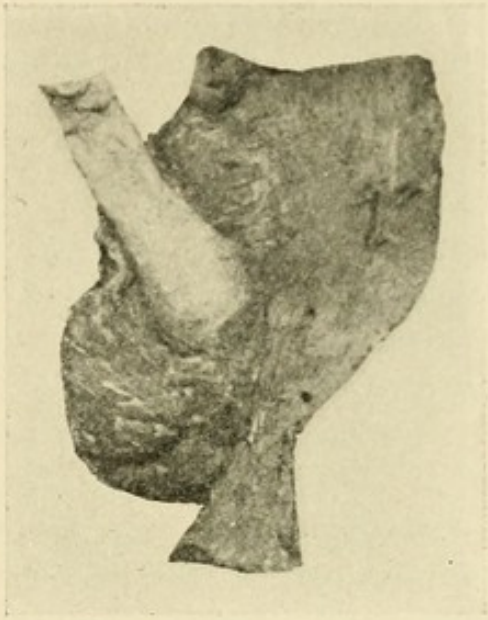


Fig. 66.—Gall-stone in the common bile-duct surrounded by the head of the pancreas (St. Thomas' Hospital Museum, 1380).

The reason for the association of the two conditions is not difficult to understand, when the anatomy of the parts is considered. Under ordinary circumstances, when a gall-stone passes along the common bile-duct and reaches the ampulla of Vater it will not only occlude the bile-passage, but also the chief excretory duct of the pancreas, the secretion of which will be retained. An infection of the retained secretion, of the walls of the ducts, and of the parenchyma of the gland, is then likely to occur, and this will continue so long as the obstruction persists.

How far the pancreatic lesion in these cases is to be attributed to the irritating action of the retained secretion, and how far to the associated bacterial infection, it is difficult to say; but it is probable that, while the former damages the tissues of the gland and renders them susceptible to infection, the process is chiefly due to the action of micro-organisms. Even when the blocking of the ducts is complete and no direct communication between the micro-organisms in the duodenum and the stagnant secretion is possible, the inflamed walls of the duct present a ready path by which infection may travel from the intestine, and that this does occur in the bile passage has been proved by aseptic ligature of the common duct. Absolutely complete blocking of the duct is, however, very uncommon, except in cancer of the head of the pancreas, for, as we shall show later, bile-pigment can be found chemically in the fæces in nearly all cases, even when the stools appear free from colour to the eye.

Another route by which infection may reach the duct of Wirsung and biliary passages has been suggested by Desjardins. We have already pointed out how, in his opinion, organisms normally find their way from the duodenum along the duct of Santorini into the main pancreatic duct, and thence into the ampulla of Vater and back to the duodenum again, and it is by this route, he believes, that infection of the biliary passages and pancreas takes place when there is obstruction from gallstones. The first effect produced by the lodging of a biliary calculus in the ampulla of Vater, or lower part of the common bile-duct, will be that the septic organisms, arriving by way of the duct of Santorini and thence passing into the duct of Wirsung, will be unable to travel into the duodenum, and, being arrested in the biliary passages and pancreatic ducts, will there set up inflammatory changes. As the pancreatic ducts are, however, more or less immune, from the constant presence in them of intestinal organisms,

the clinical symptoms will, in the first place, be referred to the bile-passages, the pancreatic ducts and the head of the pancreas not being markedly affected by the process until they are attacked by bacteria whose virulence has been increased by growing in the morbid secretion and diseased tissues of the bile-ducts. Inoculation and re-inoculation from the pancreas to the biliary passages, and back from the bile-ducts to the pancreas, will then occur, so that the pancreatic lesion will continually progress so long as the obstruction is unrelieved. This hypothesis has been accepted by Quenu and Duval. While not denying that it is in some instances possible, we would point out that, according to the observations of Opie upon the ducts, it is unlikely that infection of the retained secretions and walls of the ducts can take place in the manner suggested in at least 31 per cent. of cases, for Opie found that in 21 per cent. of the bodies he examined the duct of Santorini was impervious, and in 10 per cent., where a through channel existed, the duct of Wirsung did not anastomose with the duct of Santorini.

In a valuable paper on "The Constituent of Bile Causing Pancreatitis" Flexner has given an account of a number of experiments which throw considerable light upon the relation of cholelithiasis to both chronic and acute pancreatitis. He found that solutions of purified bile salts when injected into the pancreatic duct of animals gave rise to acute fatal hæmorrhagic and gangrenous inflammation of the gland, with fat necrosis, but that the mucigenous residue from dog-bile, precipitated out by alcohol, when similarly injected produced no lesion in seventeen days, except that there was slight sclerosis, probably from ligature of the duct. It was therefore evident that the effect of the injection of bile was due to the bile salts. On mixing the bile salts with the mucigenous residue, the lesion produced by injection was found to be of a less acute and destructive character than that

following the injection of bile salts alone. A similar result was obtained when agar and gelatine were substituted for the mucoid material. The action of the bile salts appeared therefore to be restrained by mixing it with colloid substances. Experiments with gelatine and bile salts showed that if the colloid was readily attacked by the pancreatic juice, so that the salts were brought rapidly into contact with the gland tissue, a moderately severe lesion resulted; whereas, with a substance such as agar, which is little, if at all, altered by the pancreatic secretion, the effect of the bile salts was exerted so slowly that all gross injury of the pancreatic substance was avoided. Increasing the colloid strength of bile, or of solutions of bile salts, by the addition of mucin, nucleoproteid, or even by diluting with normal saline, was found to modify the intensity of the lesion in a similar way to gelatine and agar, so that the pancreas might altogether escape injury from a quantity of bile salt which would otherwise have caused a severe and rapidly fatal condition.

Flexner concludes from these experiments that when the composition of the bile is modified by a diminution of its salts or an increase of colloid material, its passage into the pancreatic duct is likely to set up chronic pancreatitis, but when fresh unaltered bile gains entry into the duct of Wirsung, it sets up acute changes. He points out that in obstruction of the biliary passages there is a loss of diffusible salts and an increase of colloid material, and, further, that inflammation of the passages causes an accumulation of albuminous products, so that by both means the composition of the bile is altered in a direction which, according to his experiments, would tend to favour the production of chronic changes rather than acute and fulminating lesions of the gland. As we have already said, it is difficult to know how far chronic changes in the pancreas in common duct obstruction

are due to micro-organisms and how far to mechanical and purely chemical causes, but it is clear from Flexner's experiments that the influence of the bile must be taken into account. Chronic pancreatitis is often associated with very small stones, so that it is possible that bile which has been modified by inflammatory changes may have been diverted into the pancreatic duct and set up chronic inflammation in the way Flexner suggests. Even with large calculi the obstruction is rarely so complete that bile cannot find its way into the intestine, and possibly also into the duct of Wirsung, and there, by its toxic action, it may predispose the tissues to the action of bacteria. When the pancreatic duct is occluded, secretion ceases at a pressure of only a few centimetres of water, owing probably to the ease with which any fluid formed by the gland cells escapes through the alveoli into the surrounding lymph spaces, so that it is not necessary to suppose that any great amount of force is required to carry bile or other fluids into the ducts, and thence into the interstices of the parenchyma. The diffusion which naturally occurs in a stagnant fluid has also to be considered in this connection. That the entry of bile is not the only cause of the interstitial changes that are commonly found in obstruction of the ducts is shown, however, by the effects of ligature, or of introducing such substances as agar or turpentine, and some part of the process must no doubt be attributed to the altered pancreatic secretion itself.

Morbid influences may not only reach the pancreas by way of the ducts, but also through the blood-vessels and lymph stream. Pancreatitis in general infectious diseases is not common, and we have already referred to the comparative rarity of abscess of the pancreas in general pyæmia. The pancreatitis which is occasionally met with as a sequel of typhoid fever is possibly due to a specific infection travelling up the ducts, but it is not

unlikely that it may arise from the infection of the blood which is now known to be always present in that disease. In Moynihan's case, which was operated on a year and a half after the attack of fever, typhoid bacilli were isolated from the bile, and the patient's blood gave the Grüber-Widal reaction for typhoid fever. Three weeks later typhoid bacilli were still present in the bile, but at the end of five weeks it was sterile. This observation, while it suggests that the source of the pancreatic condition lay in the infected state of the bile, due to the passage of typhoid bacilli up the bile-ducts from the intestine, cannot be accepted as conclusively settling the point, for it is well known that the urine may contain typhoid organisms months, and even years, after recovery from an attack, although in this instance the infection undoubtedly reaches the kidneys, and through them the urine, by way of the blood.

Influenza and other zymotic diseases are also occasionally followed by chronic inflammation of the pancreas. In these the infection is probably carried by the blood, although in the gastro-intestinal form of influenza direct infection of the pancreas through its ducts may take place.

An attack of mumps is in some instances complicated by pancreatitis, and although the unknown causal agent is probably carried from one to the other by the blood-stream, the connection is as obscure as that which exists between parotitis and orchitis.

The influence of alcohol in the production of cirrhosis of the liver is still a debatable point, and similarly its relation to chronic pancreatitis has not been settled. In some cases a history of alcoholism can be obtained, but this is not common. It is probable that alcohol is not itself a direct determining cause, but that, indirectly, by the influence it exerts upon the circulation, and by a production of a catarrh of the duodenum, it may give rise to pancreatitis.

The chronic infections, *syphilis and tubercle*, affect the pancreas through its blood and lymph supply. Both give rise to changes in the interstitial tissue. The syphilitic lesions may be divided into those met with in congenital syphilis, and those occurring in the acquired infection.

Attention was first drawn to the frequency with which the pancreas is affected in congenital syphilis by Birch-Hirschfeld in 1875, and, although the investigations of Schlesinger, and later observations by Birch-Hirschfeld himself, have shown that it is not so common as he had at first supposed, it is by no means uncommon, and would appear to be present in about 22 or 23 per cent. of all cases of syphilis in new-born infants. The condition, like many other syphilitic lesions, is due to an overgrowth of the interstitial tissue, which, according to Schlesinger, originates about the blood-vessels. The inflammatory new-growth affects both the interlobular and interacinar tissue, and occasionally spreads between the acinar cells, which atrophy and disappear without presenting any evidences of degeneration. In the two cases of congenital syphilitic pancreatitis examined by Opie, numerous

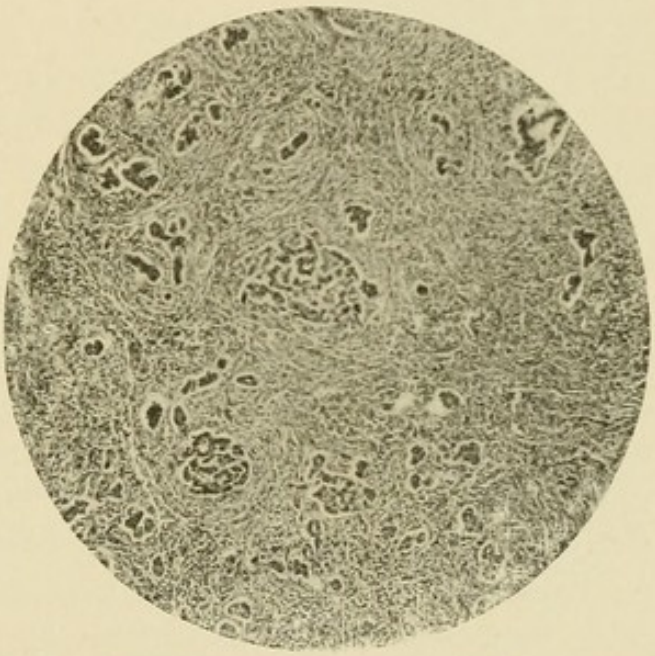


Fig. 67.—Congenital syphilitic pancreatitis, with almost complete destruction of the secreting acini and persistence of the islands of Langerhans (× 50) (Rolleston's case).

islands of Langerhans were present in the thickened stroma, and some were found to be in connection with the secreting structure of the gland, although the lumen of the duct could be traced no further than the periphery of the island. Schlesinger has also pointed out that the islands of Langerhans are neither invaded by the new-growth of interstitial tissue nor implicated in the atrophy which affects the cells of the acini.

Opie mentions that the parenchyma in his cases presented the appearance observed about the fifth month of development, save that the islands of Langerhans were more marked features in the syphilitic glands. An explanation of the similarity between the undeveloped and syphilitic organ is afforded by supposing that the development of the individual cell is not retarded, and that the changes in the parenchyma result, not so much from its destruction, as from interference with its growth. The islands of Langerhans being the result of an early cell-differentiation, and lying more or less in the centre of the masses of secreting cells, where they are protected from the early results of the overgrowth of connective tissue, develop and remain unaffected by the interstitial changes until a late stage of the disease. Birch-Hirschfeld believed that congenital syphilitic pancreatitis affected the organ during the last months of fœtal life, but Schlesinger concludes from a study of his own cases, and those of Mraczek and Müller, that it may be affected as early or as late as other organs.

Syphilitic lesions in acquired syphilis are much rarer than in the congenital form of the disease, although Hansemann, Kasahara, and other writers have contended that it is the most common cause of chronic pancreatitis. A few cases of indurative pancreatitis, due to acquired syphilis, have been recorded, but the condition most frequently met with is the penetration of the parenchyma by irregular bands of scar-like tissue and gummata.

Occasionally, as in the case reported by Drozda, the pancreas may be converted into a mass of indurated tissue in which only remains of the gland substance can be found. Betham Robinson has reported a case of obstructive jaundice due to gummatous infiltration of the head of the pancreas, in which cholecystcolostomy was successfully performed. In a few cases of congenital syphilis minute and rarely large gummata have been noticed.

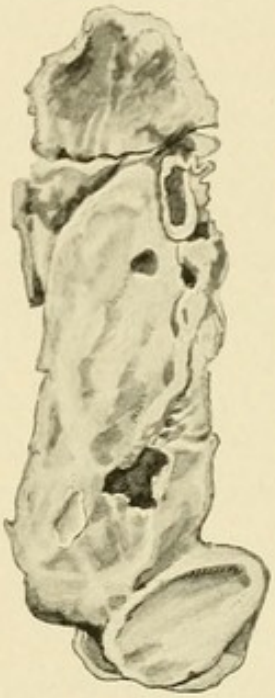


Fig. 68.—Tuberculosis of the pancreas following tuberculous meningitis, showing deposits of tubercle and a small abscess cavity (St. Bartholomew's Hosp. Museum, 2272 A).

Tuberculosis of the pancreas arises practically always in connection with tuberculosis in other organs, the blood-vessels furnishing the channel by which the bacilli are distributed to the gland in the majority of instances. Primary tuberculosis of the pancreas was probably present in a case of Senn's described by Mayo, but it is the only one of which we can find any record. Multiple small tuberculous deposits may be found irregularly scattered through the substance of the gland, or single large masses, which may caseate and form cavities that open into adjacent organs, such as the stomach, may be met with. It is probable that the single masses originate from the lymph glands buried in the substance of the organ, for such a mass was successfully removed by operation from the head of the pancreas by Sendler, and on microscopical examination was found to be a tuberculous lymph gland.

According to Carnot, diffuse interstitial pancreatitis is more commonly associated with tuberculosis of other organs than is the specific lesion itself. Cases of this

description have been reported by Carnot, Ancelet, Vulpian, Arnozan, Morache, and Opie. There is usually a moderate degree of chronic inflammation, causing an increase of the connective tissue normally present around vessels and ducts and between the lobules. By injecting considerable quantities of a suspension of tubercle bacilli into the ducts and parenchyma of the pancreas in dogs Carnot was able to produce caseous abscesses and inflammatory changes, but the lesions showed none of the specific characters of tuberculosis, and tubercle bacilli were not found in the tissues. Inferring from these results that the changes noticed might be due to the action of the toxines contained in the organism, he injected tuberculin, prepared from dead bacilli, into the parenchyma of the gland, and obtained in one instance localised sclerosis. That chronic pancreatitis may be caused by chemical products elaborated in a tuberculous lesion is also suggested by cases described by Carnot and Arnozan. In the former the splenic extremity of the gland, in contact with a tuberculous kidney, was alone affected, and in the latter chronic pancreatitis accompanied tuberculous peritonitis.

Alterations in the blood supply of the pancreas are another cause of chronic interstitial changes. General arterial sclerosis and endarteritis, although more commonly associated with atrophy and fatty degeneration, sometimes give rise to chronic interstitial pancreatitis. It is possible that the moderate increase of fibrous tissue found microscopically in a certain number of patients over forty years of age (10 per cent. of Bosanquet's cases) may be due to this cause. Fleiner suggests that the condition is similar to that met with in contracted kidney, and in the liver, brain, and heart, as a result of endarteritis obliterans. Both he and Hoppe-Seyler think that the arterial disease causes nutritive changes in the parenchyma, which degenerates and is replaced by fibrous

tissue. An increase of the connective tissue of the gland, especially that connected with the veins and lymphatic vessels, has been described by Lepine, Abia, Lemoine, and Lannois. In these cases the lobules were separated by strong trabeculæ of connective tissue which penetrated between the individual cells. In spite of the marked microscopical changes found, it is noteworthy that no abnormality of the pancreas was seen on naked-eye examination. Long-standing difficulty of venous flow, due to chronic disease of the heart, liver, lungs, etc., may cause induration and fibrosis of the pancreas, as of other organs. Thrombosis, or blocking of the portal vein by growth, has also been met with as a cause of chronic changes in the pancreas. Basing his conclusion on the post-mortem records of Guy's Hospital, Hale White is of opinion that disturbances of circulation are much commoner than other causes of cirrhosis, congestion, or hardening of the pancreas. Opie, however, comes to the conclusion that chronic passive congestion is an unimportant factor in the production of chronic pancreatitis, and in our experience circulatory disturbances are uncommon clinical causes of pancreatic troubles.

Nearly all modern observers are agreed that the pancreas is frequently affected by an overgrowth of connective tissue in *cirrhosis of the liver*. In cases associated with portal cirrhosis the size of the pancreas varies. It is generally enlarged as a whole, but should atrophy recognisable by the naked eye be present, the body and tail of the gland are the parts chiefly affected. Klippel and Lefas found that the size and consistency of the pancreas are not related in any way to the condition present in the liver. As a rule, the liver is more seriously affected, but in some cases the disease of the pancreas is in a more advanced stage. In every case, however, the fibrous tissue in the pancreas was fully formed and poor in nuclei, even when the newly formed fibrous tissue in

the liver was of a semi-adult type. They therefore conclude that cirrhosis of the liver and pancreas are due to the same etiological factors, but that the pancreatic condition is independent of, and not secondary to, the lesion in the liver. The increase of fibrous tissue in the pancreas is perilobular, intralobular, or partly periacinous, but is usually chiefly intralobular. There is occasionally interlobular œdema, and scattered areas of small-celled infiltration are met with. The gland cells show fatty and pigmentary changes, but the islands of Langerhans are unaffected.

Although the pancreas in biliary cirrhosis is not generally increased in size or weight, it is often indurated, and may be united to neighbouring organs by adhesions. The fibrosis is of an embryonic type, and appears to spread from the ducts. The acinar cells show signs of fatty degeneration, and there is some proliferation of the cells lining the ducts. Exceptionally there may be enlargement of the pancreas with hypertrophic cirrhosis of the liver, when there is also extreme enlargement of the spleen.

Chronic interstitial pancreatitis is met with in *hæmochromatosis*. In this condition the pancreas is enlarged, firm, and pigmented, there is generally hypertrophic cirrhosis of the liver, and, in the majority of cases, bronzing of the skin also occurs. The islands of Langerhans are gradually altered or destroyed, and diabetes (*diabètes bronzé*) usually supervenes in the later stages. The etiological factors of this disease are not known, but it is evident that they simultaneously produce change in the liver and pancreas.

Occasionally chronic inflammation of the pancreas may be due to the *extension of inflammatory processes* from neighbouring organs. The most common origin is from a gastric ulcer adherent to the head of the gland. Ulcers of the duodenum, and ulcerating malignant growths

of the pylorus, have also been responsible for the condition in our experience. Cases in which secondary inflammation has been caused by ulcerating growths in other organs, by pre-vertebral inflammatory processes, and by aneurysm of the aorta or cœliac artery, have been recorded.

From what has been already said on the microscopical appearances seen in chronic pancreatitis arising from various causes, it will have been gathered that the histological changes are not always of the same type. A classification of the various forms based upon etiological data is, in the present imperfect state of our knowledge, unsatisfactory, and similarly attempts to refer the origin of the fibrous overgrowth to the ducts, blood-vessels, and lymph channels are so speculative as to be unreliable in practice. The best working classification is that first clearly outlined by Opie. This observer distinguishes two main types of chronic interstitial inflammation, which can be distinguished microscopically, and present more or less different characters to the naked eye. In the first, or "*interlobular*" type, the increase of connective tissue, although never accurately confined to one locality, is most conspicuous between the lobules, and affects little, if at all, the intralobular and interacinous trabeculæ. The normally obscure lobulation of the gland becomes more conspicuous, and wide bands of sclerotic tissue separate groups of lobules. The progress of the lesion is apparently inward from the periphery of the lobules, which are invaded to a greater or less degree by the newly formed fibrous tissue. Often entire lobules are seen in the process of disintegration and replacement. The islands of Langerhans are not affected until a late stage of the disease and diabetes does not occur, except when the fibrosis is very advanced. Macroscopically the gland is hard and dense, and has a nodular or granular surface when the lesion is well marked. On section the

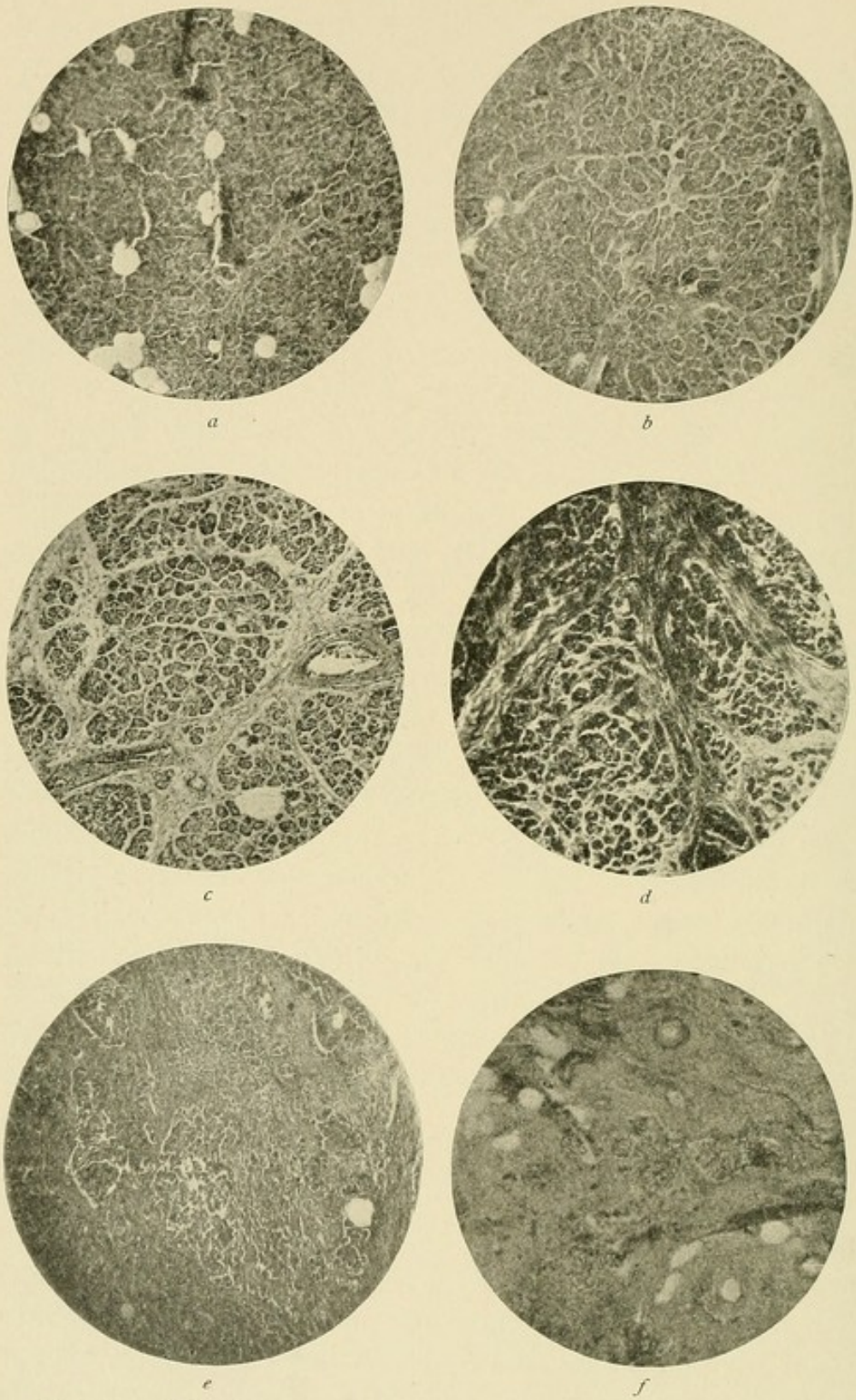


Fig. 69.—Microphotographs of the pancreas in six cases of chronic pancreatitis under our care, showing the stages of the process: (*a*) Catarrhal pancreatitis; (*b*) slight interlobular pancreatitis; (*c*) more advanced interlobular fibrosis; (*d*) advanced interlobular pancreatitis; (*e*) very advanced fibrosis; (*f*) cirrhosis of the pancreas from a case of diabetes (× ca 42).

loose areolar tissue, normally present between the secondary and tertiary lobules, is found to have been replaced by sclerotic bands, so that the cut surface has a compact and homogeneous appearance.

In the second, or "*interacinar*" type, the new-formation of fibrous tissue takes place primarily within the lobules, is of a diffuse character, and forms an irregular network of fibrous strands of varying thickness which encloses the gland acini in its meshes. The interlobular tissue may be only slightly altered. The islands of Langerhans are early affected, and diabetes is a common accompaniment of the condition. The organ is usually smooth on the surface, and in section is found to be tough rather than hard. Well-marked microscopical changes may be present, in either form, however, without there being any noticeable macroscopical lesion.

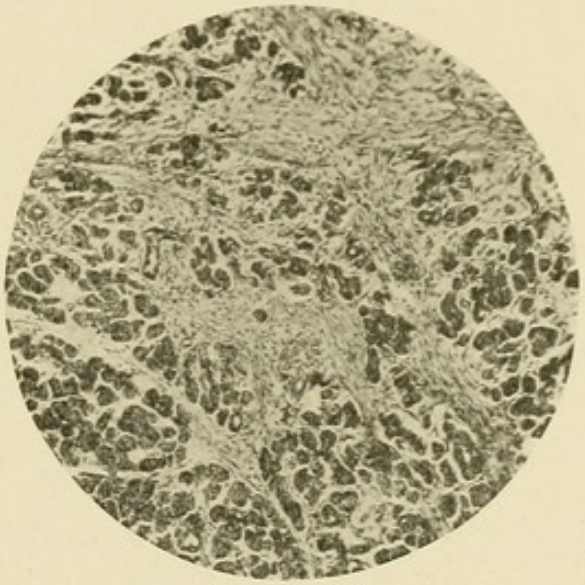


Fig. 70.—Interstitial pancreatitis in the neighbourhood of an adherent gastric ulcer (× 40).

Calculi.—An extreme degree of sclerosis is often found to be associated with the presence of pancreatic calculi in the ducts, and it is usually assumed that the pancreatitis is a result of the blocking and irritation of the ducts by the calculi. Although this is no doubt true to a certain extent, and the very marked fibrosis found post-mortem in such cases is largely due to the presence of the calculi, it is probable that the concretions themselves arise as a consequence of morbid changes in the pancreatic secretion con-

nected with inflammatory changes in the glands and ducts. By ligaturing the duct of Wirsung, Pende was able to induce the formation of pancreatic calculi in a considerable proportion of the rabbits on which he operated. The concretions were small, and none were discovered until a minimum interval of twenty-eight days had elapsed. They consisted of a deposit of calcium carbonate in an

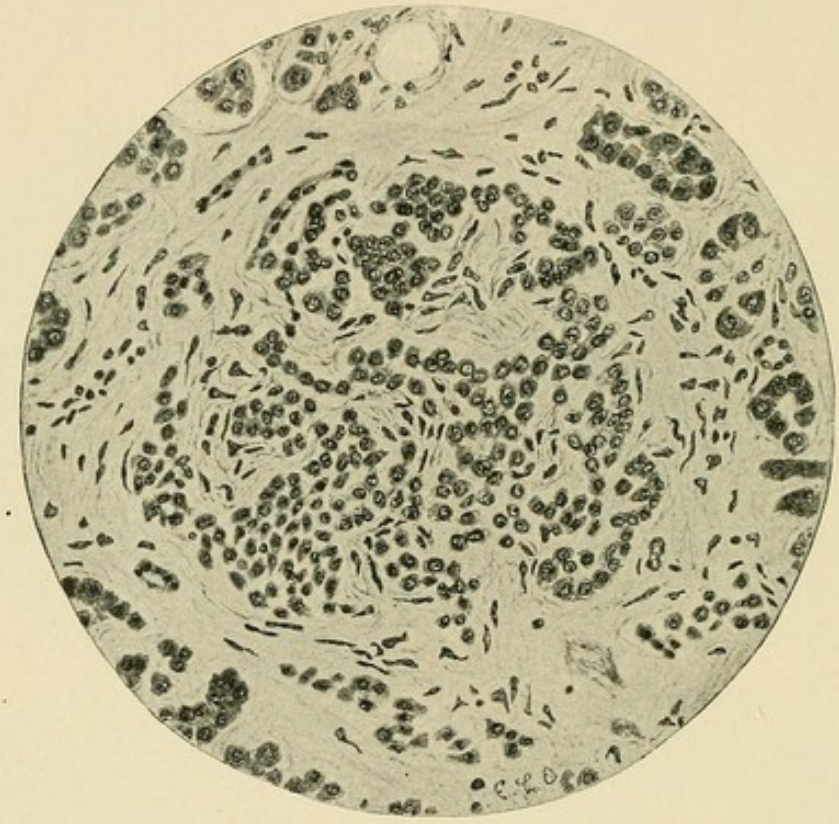


Fig. 71.—Chronic interstitial pancreatitis of interacinar type, showing the invasion of an island of Langerhans by the inflammatory process (Opie).

organic matrix, and contained no appreciable amount of phosphates, thus agreeing with the composition of many pancreatic calculi obtained from man. These are often found to contain 50 per cent. or more of calcium carbonate with traces of magnesium, some organic matter, mainly of a proteid nature, and of phosphates a varying amount or none at all. According to this observer, therefore,

simple obstruction of the pancreatic duct is sufficient to produce pancreatic lithiasis. Desquamation of the epithelium of the ducts is the primary effect; the cellular elements then lend themselves to the formation of a fibrillar network which forms a nucleus for the precipitation of calcium carbonate. This salt, which is absent from the normal secretion, appears as a result of the chronic irritation due to the stasis, which also leads to a reaction in the pericanalicular, interacinar, and interlobular connective tissue of the gland. Thiroloix has also produced lithiasis in the pancreas of a dog experimentally

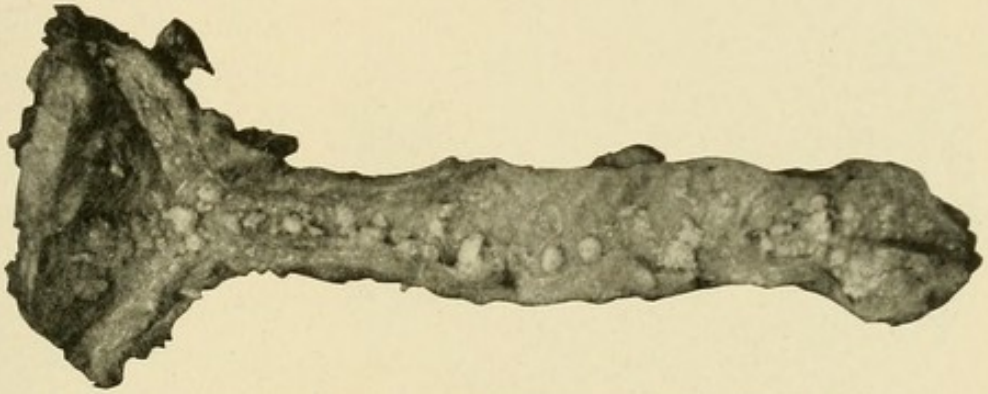


Fig. 72.—Pancreas from a case of pancreatic calculi, laid open to show the calculi lying in the dilated duct of Wirsung and the attendant atrophy of the gland due to the associated inflammatory changes, from a case of diabetes (Leeds Museum, E E 202).

by injecting a mixture of soot and carbolized liquid vaseline into the duct of Wirsung, after the duct of Santorini had been tied. Post-mortem the pancreas was found to be sclerosed, and in the tail a large cystic cavity, containing clear, watery fluid, and surrounded by chronic inflammatory tissue, had developed. In the cyst, and in the duct also, small, hard, irregular concretions had formed. The view that gall-stone formation is due to the influence of micro-organisms has been gaining ground since Bernheim directed attention to the connection between typhoid fever and cholelithiasis in 1880, and Galippe found bacteria in the interior of biliary calculi

in 1886. This has naturally led some, and particularly Nimier, to attribute to micro-organisms a causative influence in the production of pancreatic calculi. The coexistence of biliary and pancreatic calculi in a case reported by Kinnicutt was thought by this observer to point to a common cause in the shape of an infection travelling up the biliary passages and pancreatic duct. Galippe on examining a stone found numerous bacteria, and Guidiceandra discovered an organism very similar to, if not identical with, bacillus coli communis in two pancreatic calculi. The concretions experimentally produced by Pende were, however, sterile, and the secretion which had been retained in the duct and its tributaries by the occluding ligature gave no growth on culture.

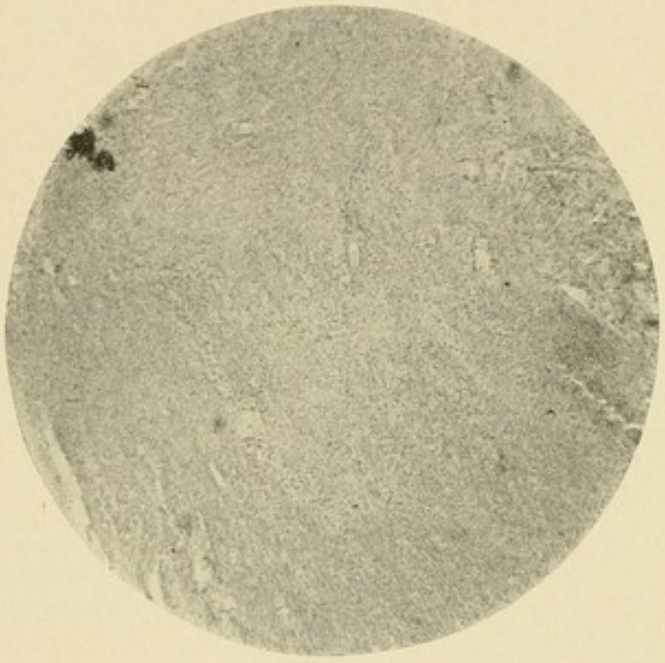


Fig. 73.—Section of the pancreas shown in Fig. 72, demonstrating complete replacement of the glandular parenchyma by fibrous tissue (× 50).

Cysts.—Experimental work on the pancreas has not thrown much light upon the etiology of the cysts occurring in that organ. Our present knowledge has been obtained chiefly on the operating table and at the bedside, and to a less extent in the post-mortem room. Senn found that ligature of the pancreatic ducts in animals caused only a moderate dilatation beyond the point of constriction, but no true cyst formation. He points out that possibly

chronic, or intermittent, obstruction might result in the production of cyst, just as ligature of a ureter, or acute obstruction, leads to atrophy of the kidney, while chronic obstruction, or obstruction of an intermittent character, tends to the development of hydronephrosis. It is probable, therefore, that the simple so-called retention cysts of the pancreas do not result solely from a hindrance to the outflow of the secretion, but that some other factor is also involved. Heinricus suggests that there is some change in the pancreatic juice, probably arising from its admixture with pathological non-absorbable products, and lessened absorptive power on the part of the vessels. The experiment of Thiroloix, already referred to, lends support to the first part of the suggestion, for in that instance a cyst of the pancreas resulted from ligature of the ducts and alteration of their contents by the injection of carbolized vaseline and soot. It will also be remembered that Thiroloix tied both the duct of Wirsung and the duct of Santorini. This is an important precaution to take, for in some instances the latter may act as a safety-valve when the main duct is obstructed. Examination of the pancreas after death in this experiment showed that it was very hard and deeply sclerosed from chronic inflammatory changes. Chronic pancreatitis is also present in many cases of simple cyst of the pancreas in the human subject, and there is no doubt, both on experimental and clinical grounds, that it is a frequent,

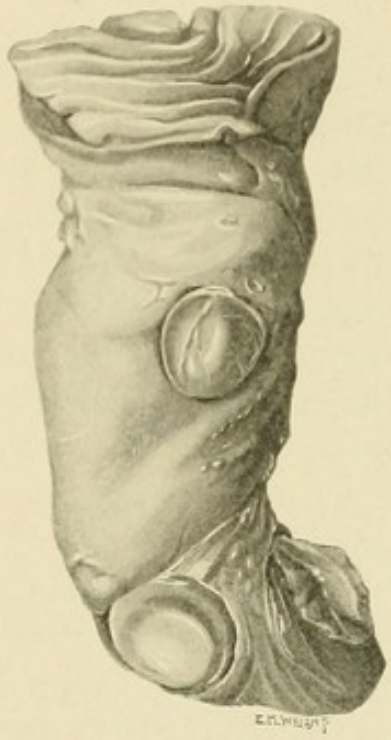


Fig. 74.—Pancreas with small retention cysts (Leeds Path. Museum, E E 203).

and probably the most common, cause of the condition. Contraction of the newly formed fibrous tissue may cause constriction of the ducts in places, while in other parts they may be pulled upon and dilated; the pancreatic secretion will then tend to collect in the dilated portions and undergo chemical changes by which its physical characters are altered, and its absorption interfered with, as Heinricus suggests.

Pancreatic calculi, as Thiroloix's experiment showed, may originate under conditions similar to those that give rise to pancreatic cysts, and both are intimately associated with chronic pancreatitis. It is probable, therefore, that when cysts and calculi occur together, as is sometimes the case, the one is not the cause of the other, as is generally assumed, but that both originate from the same pathological process. Blocking of the excretory duct by a calculus is, however, likely to bring about more rapid distension of any cystic cavity that may be present and so increase its size as to make it clinically recognisable.

A gall-stone impacted in the ampulla of Vater has been quoted as the cause of retention cysts of the pancreas in some cases, and although the blocking of the pancreatic duct in this way may bring about the distension of a small pre-existing cyst in a similar manner to a pancreatic calculus in the duct itself, it is not likely that the obstruction is the primary cause of the cyst formation. Gall-stones and chronic pancreatitis are very frequently associated, and in some instances the two conditions may be due to the same infective process, so that in this instance also the calculus is possibly but the secondary cause that brings into clinical prominence cysts previously formed as the result of chronic inflammatory changes in the gland.

Repair following traumatism, duodenal ulcers, tumours in the bile-passages or duodenum, swollen lymphatic glands, and even intestinal parasites in the pancreatic

duct are all liable to be accompanied by chronic pancreatitis, and have each been met with in association with cysts of the pancreas. Whether they are to be regarded as the primary causes of the cysts, or merely as secondary factors accentuating a pathological state arising from the inflammatory changes in the gland, it is difficult to say, but in our opinion the latter is the more probable explanation, at least in many instances.

It has been contended by some writers that cysts of the pancreas may originate from extravasations of blood, either within or without the gland, and Hagenbach has distinguished between "hæmatoma," in which bleeding occurs into a pre-existing cyst, and "apoplectic cysts," resulting from hæmorrhage into softened, degenerate gland-substance. The distinction is, however, not recognised by most modern authorities, and the presence of a large amount of blood in a pancreatic cyst is now generally regarded as merely the result of a more marked hæmorrhage into the cyst cavity than usual.

Retention cysts may be single or multiple, unilocular or multilocular. Two cysts of almost equal size may be present simultaneously, or one cyst may be found with a number of smaller ones attached to its walls. Obstruction of the main duct near its entrance into the duodenum may cause a rosary-like dilatation to which Virchow has given the name of "ranula pancreatica." Dilatation of part of the main duct tends to give rise to a spherical or oblong swelling, while obstruction of the smaller ducts may result in the formation of the collection of minute cysts spoken of by Klebs as "acne pancreatica."

As a cyst enlarges it encroaches upon and destroys the substance of the gland, or, growing away from the pancreas, it may become pedunculated. The size varies within very wide limits, from the tiny points of fluid met with in acne pancreatica, to enormous tumours holding fifteen or twenty litres of fluid. The wall of a simple

retention cyst is composed of dense fibrous tissue, poor in cells, and is generally from 3 to 4 mm. in thickness. The inner surface may be smooth, shining, and free from epithelium, or be covered with a layer of cylindrical cells resembling those lining the ducts. Indications of the formation of the larger cysts by the fusion of smaller cavities may be met with in the shape of projections of, or septa on, the inner surface, and portions of pancreatic tissue are not infrequently found embedded in their walls. The outer surface is often traversed by large distended blood-vessels.

The contents of these cysts are of a fluid character, but vary considerably in their appearance and properties. The colour is generally dark reddish-brown, but may be yellow, greenish, milky, or even bright red, from recent hæmorrhage. The fluid is usually viscid, generally more or less turbid, and of a specific gravity of 1.007 to 1.028. It is generally alkaline in reaction, is rarely neutral, and in one instance, reported by Bozeman, was acid. Albumin, as might be expected from the very frequent presence of blood, is a constant constituent. Sugar has been met with in rare cases; 2.7 per cent. was found in a case of diabetes recorded by Bull. In Hoppe's case the fluid contained 0.12 per cent. of urea.

Microscopical examination generally shows blood-cells, fat, and epithelial cells, often cholesterin, and rarely leucin and tyrosin (Tilger, Newton Pitt, and Jacobson). In many of the recorded cases one or more of the pancreatic ferments have been detected, but they have not been invariably found, and have indeed been proved to be absent in cases of undoubted pancreatic cyst, confirmed by post-mortem examination.

Proliferation cysts, or *cystic neoplasms*, of the pancreas are very much rarer than the form just described. They may be either simple or malignant, although some cannot be relegated to one or the other category on

histological grounds alone. The simple proliferation cyst, or "cystadenoma," is usually multilocular and has a lining of columnar epithelium, which is sometimes seen to dip down into the wall of the cyst in the form of a gland, and often covers polypoid masses projecting into the cavity of the cyst. The malignant form, or "cystic epithelioma," occurs as a series of small cysts, or a polycystic mass, showing patches of carcinomatous material in the walls. The cells of the solid portions of growth are arranged in irregular groups, devoid of any true glandular order, and are large polyhedral and often multinuclear. In Hartmann's case the tumour is reported to have contained 200 grams of chocolate-coloured fluid. Metastatic deposits may be found in the liver, pancreatic glands, duodenum, and in other situations. The formation of cysts in cancer of the pancreas has been described by Roux.

It has been suggested that tumours arising in the neighbourhood of the pancreas, and closely resembling multilocular proliferation cysts of that organ, may arise from remnants of the Wolffian body and be mistaken at operation for pancreatic growths. Monprofit has published a case in which a large cystic tumour was so firmly attached to the spleen and the tail of the pancreas that it was necessary to remove both to complete the operation. From the microscopical characters and situation of the growth it was concluded that it had originated from remains of the Wolffian body in the posterior layer of the mesocolon. Dunning has also reported a somewhat similar case. Invasion of the substance of the pancreas by such growths, or by similar neoplasms in the left suprarenal capsule, may readily be mistaken at operation for a growth of the pancreas, and the presence of adherent remains of the pancreatic tissue may tend to confirm the error on microscopical examination.

Hydatid cyst and congenital cystic disease of the pan-

creas are both exceedingly rare. They differ in no essential particular from similar lesions met with in the liver, kidneys, and elsewhere.

Pseudo-cysts, as Körte has proposed to call them, constitute a large proportion of the cases reported as pancreatic cysts. They are fluid tumours found in more or less close proximity to the pancreas, but not originating

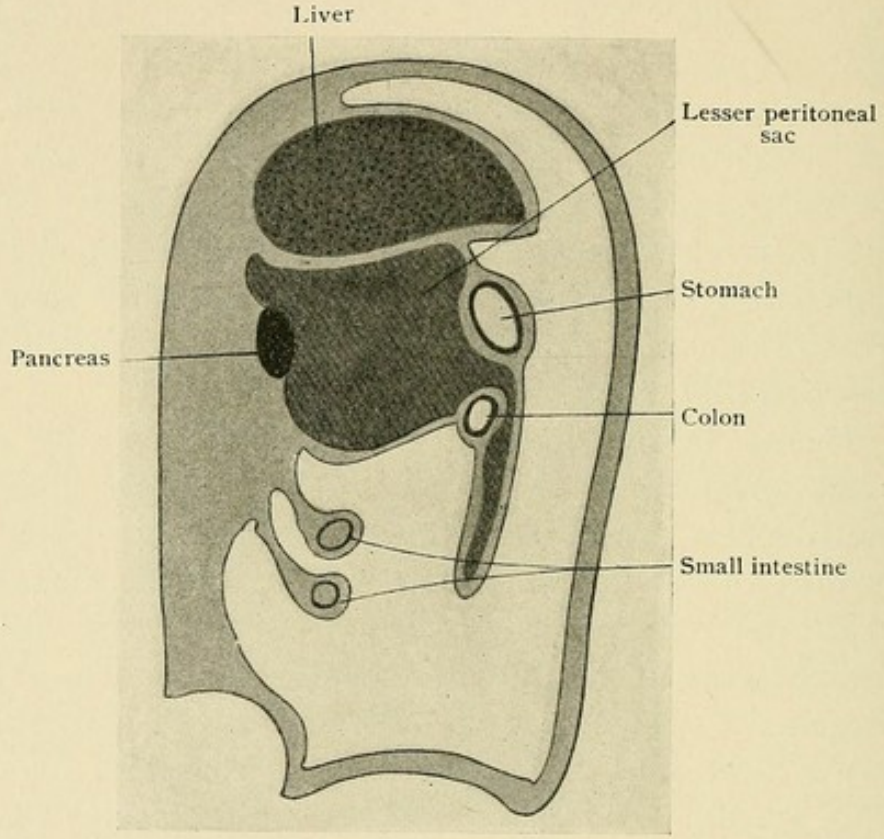


Fig. 75.—Diagram to show the method of origin of a pseudo-cyst of the pancreas.

in the substance of the gland. The most frequent form is that described by Jordon Lloyd, in which an effusion takes place into the lesser peritoneal cavity, mainly as the result of injury of the pancreas. The escape of blood, followed by pancreatic juice, into the lesser cavity of the peritoneum sets up a mild form of peritonitis which may close the foramen of Winslow and produce a tumour, which,

during life, it is impossible to distinguish from a true pancreatic cyst. The fact that a cavity within the abdomen contains a fluid possessing digestive powers is no proof that it is a retention cyst, but merely that it is probably connected with the pancreas. Other forms of pseudo-cyst will be considered in connection with the diagnosis of swellings of the pancreas, but it may be mentioned here that the greater proportion are met with in males, who are more exposed to injury, whereas the majority of true cysts appear to occur in women.

The relation of trauma to cysts of the pancreas has been debated by Körte, Tilger, Moynihan, and others. Körte has described two classes of traumatic cysts of the pancreas, one in which, after long-continued discomfort in the epigastrium, a tumour gradually develops, and the other where, within a short time of the injury, a tumour of considerable size has formed. In the former it is possible that the injury leads to a chronic interstitial inflammation, such as is known to follow experimental injury of the pancreas in dogs, and that this gradually gives rise to cyst-formation in the manner already described. In the latter class of cases, where the tumour forms rapidly, and increasing up to a certain point, then remains stationary, the effusion is probably poured out into a pre-existing cavity, such as the omental bursa, and is a form of pseudo-cyst.

Tumours.—The solid tumours met with in the pancreas are carcinoma, sarcoma, adenoma, and lymphoma. It was formerly taught that carcinoma is the most frequent of all diseases of the pancreas, and although it is the most common new growth, it is certainly not the commonest lesion. The mistake has arisen from too great reliance being placed upon naked-eye observation in the post-mortem room, and the failure of surgeons in the past to recognize that many swellings of the head of the pancreas associated with jaundice are merely inflammatory. The

importance of the latter point was strongly insisted upon by one of us in 1900, and has since been confirmed by a number of independent observers.

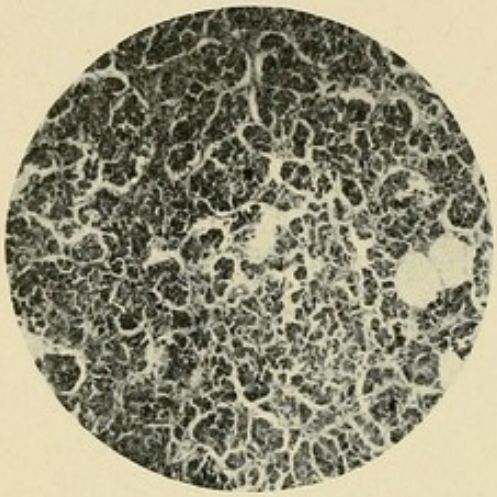


Fig. 76.—Spheroidal-celled carcinoma of the pancreas (× 50).

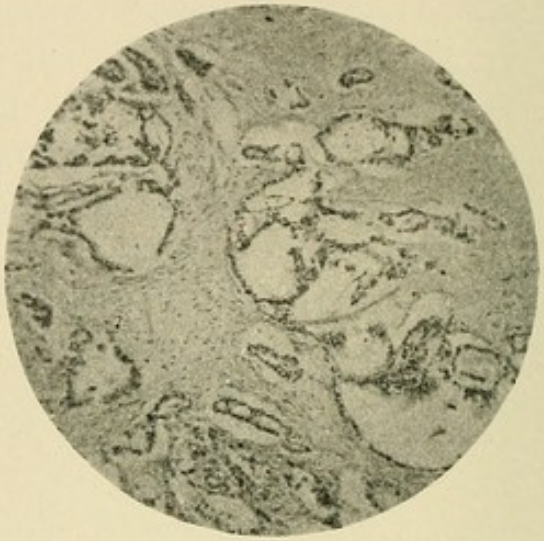


Fig. 77.—Columnar-celled carcinoma of the pancreas (× 50).

Fig. 78.—Columnar-celled carcinoma of the pancreas (× 150).

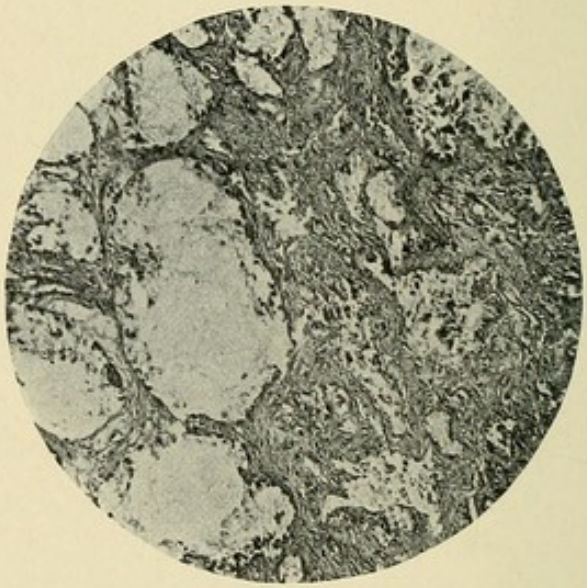


Fig. 79.—Columnar-celled carcinoma of the pancreas undergoing colloid change, from a case of diabetes (× 40).

Primary carcinoma of the pancreas may begin in the glandular epithelium, or in the cells lining the excretory

ducts. In the former case it is of the spheroidal, and in the latter is generally said to be of the columnar, type. Letulle, however, maintains that primary carcinoma of the duct of Wirsung is spheroidal and not columnar celled. Spheroidal-celled carcinoma is, at any rate, much the more common, and is usually of the scirrhous variety. Encephaloid tumours are sometimes met with, and rarely a colloid carcinoma, resulting from degenerative changes in a columnar-celled growth, has been encountered. Hillier and Goodall have distinguished a variety of carcinoma characterised by great irregularity in the size and shape of the cells, which they believe arises in the island of Langerhans.

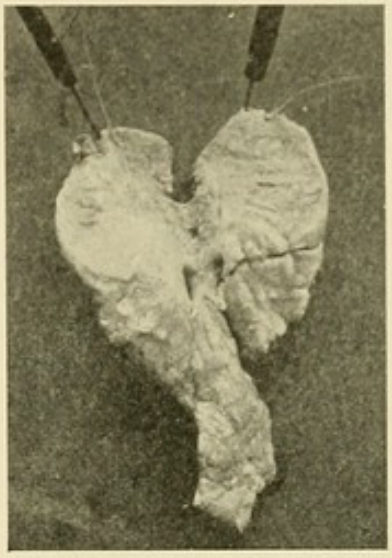


Fig. 80.—Cancer of the head of the pancreas (St. George's Hospital Museum, 201 B).

The most frequent site of the lesion is in the head of the gland, some 62 per cent. of the recorded cases being in that position. In about 5.5 per cent. the tail of the organ was most affected, in 3.5 per cent. the body, and in 29 per cent. there was a diffuse growth involving, more or less, the whole of the pancreas. The duct of Wirsung is compressed by the growth in nearly all instances. Courvoisier found it obliterated in 55 out of 66 cases, and, according to Boldt, it is dilated beyond the point of stricture in one-third of all cases of malignant disease of the head of the gland. Growth in this situation almost always causes gradually increasing, painless jaundice with enlargement of the gall-bladder, points of some importance in the diagnosis of the condition from obstruction of the duct due to gall-stones, in which, although there may be equally deep jaundice, there is commonly a history of

pain and the gall-bladder is small and shrunken. The

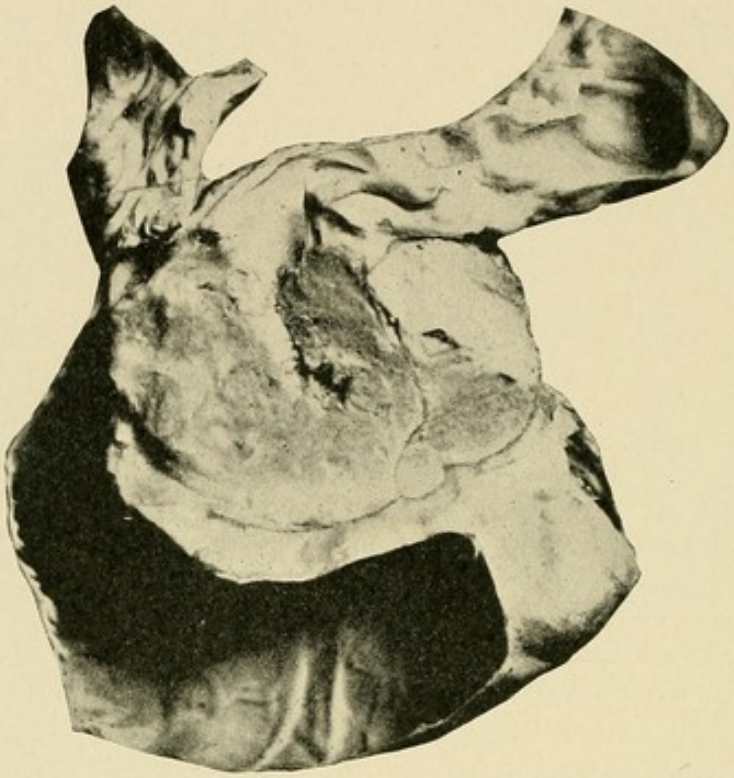


Fig. 81.—Cancer of the head of the pancreas showing dilatation of the duct of Wirsung (St. Thomas' Hosp. Museum, 1415).

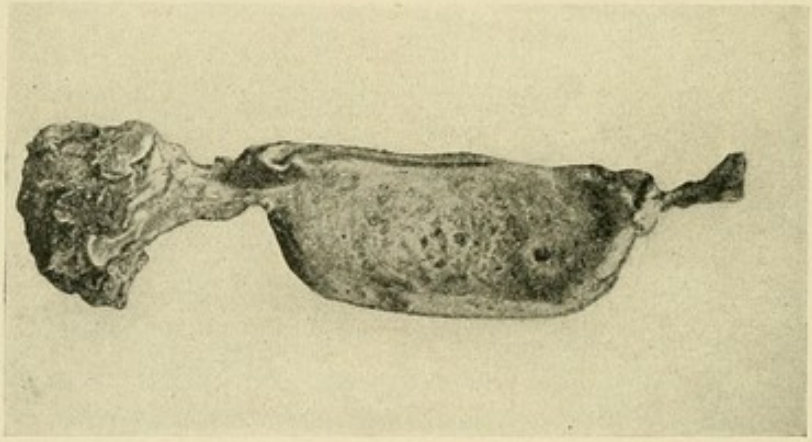


Fig. 82.—Carcinoma of the body of the pancreas (Royal Coll. of Surg. Museum, 3835).

explanation of the different behaviour of the gall-bladder in the two conditions appears to be that, as

the result of gall-stone irritation, it frequently becomes diminished in size and adherent, so that when the common duct is subsequently blocked, it is unable to expand, whereas blocking of the duct by a tumour at once causes distension of the gall-bladder, for it has not been altered by previous inflammatory changes. It has also to be remembered that, although the obstruction due to a large gall-stone may possibly be absolute at first, it quickly ceases to be so, and small quantities of bile find their way into the intestine, but that in malignant disease of the head of the pancreas the obstruction gradually increases, and eventually becomes absolute, so that not a trace of stercobilin can be found in the fæces. The backward pressure in the ducts in these cases, while it prevents the excretion of bile, does not interfere with its formation, and it is consequently absorbed by the lymphatics and gives rise to jaundice. The pressure in the ducts also prevents the bile reaching the gall-bladder and it is consequently found to be only filled with mucus.

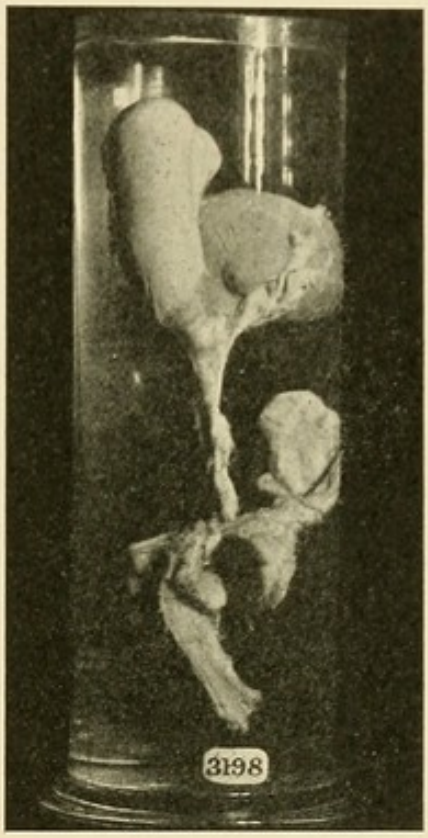


Fig. 83.—Cancer of the head of the pancreas producing dilatation of the common bile-duct and gall-bladder (Univ. Coll. Hosp. Museum, 3198).

The relations and size of some of these growths explain the compression and perforation of the duodenum, stomach, colon, ureter, portal vein, aorta, vena cava, splenic artery and vein, and superior mesenteric vein that sometimes take place.

Secondary deposits occur most frequently in the liver, but may be found anywhere, or indeed everywhere, for Oser has reported general carcinomatosis from a pancreatic growth, although the primary origin of the growth is perhaps rather a matter of surmise in such cases. As in carcinoma elsewhere, carcinoma of the pancreas is most frequent after the fortieth year. Bohn has, however, reported the occurrence of the disease in a child of seven months, Kuhn in one of two years, and Dutil in a patient fourteen years of age.

In many cases of primary carcinoma there is a coexisting fibrosis of the gland, and, although it is probable that in many instances the overgrowth of fibrous tissue results from the inflammatory changes set up by the spread of the tumour, it is possible that, in some, the fibrosis may have been the primary condition, and that the carcinoma may have originated in groups of cells isolated by the fibrous tissue, in much the same way as primary cancer of the liver appears to arise from groups of cells similarly isolated in cirrhosis of that organ. The frequent association of chronic pancreatitis with cholelithiasis has already been insisted upon, and it is not unlikely that gallstone trouble may thus be a cause of cancer of the pancreas. The very high proportion of cases in which the primary growth is situated in the head of the gland tends to favour the view that there may be some such association.

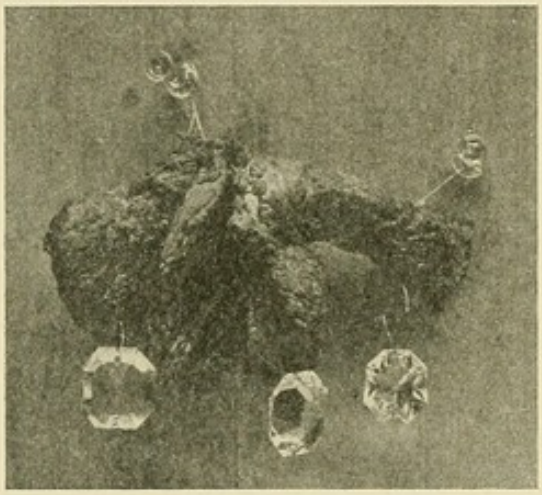


Fig. 84.—Colloid carcinoma of the pancreas (St. George's Hosp. Museum, 201 D).

Primary sarcoma is very rare. Segré met with only two cases in 11,492 post-mortems, and Hale White mentions only one, of undoubted primary sarcoma, in 6708 autopsies at Guy's Hospital. In most instances, where a histological examination has been made, the growth has been described as a small round-celled sarcoma or a lymphosarcoma, but it is doubtful whether some of these can be regarded as truly primary growths of the pancreas, for although the pancreas was deeply involved, the lymphatic glands, duodenum, or other structures have also been affected. A very large spindle-celled sarcoma of the pancreas is preserved in University College Hospital Museum (No. 3200), and mixed-celled sarcomas have been described by Healey and by Kakels. The pancreatic tumour in the former case consisted chiefly of round cells, but in some parts groups of mixed cells were seen, while the secondary growths, which were present in the liver, were chiefly of the large spindle-celled variety. Kakels' case was a very vascular mixed-celled sarcoma in the tail of the gland, and, according to him, is only the third authentic case of a primary sarcoma in that situation. Krönlein and Lubarsch have each reported a case of angiosarcoma. A sarcoma of the pancreas, in which typical epithelial proliferations were found in the growing parts, has been described by Michelsohn, and a similar case of "sarco-carcinoma" has been reported by Baudach. Briggs removed an old hydatid cyst from the pancreas of a woman the walls of which, on microscopical examination, were

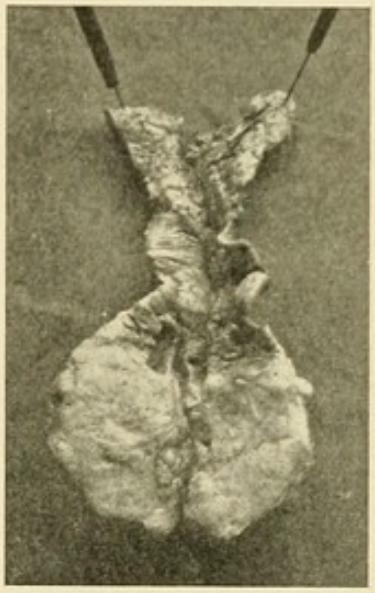


Fig. 85.—Sarcoma of the pancreas (St. George's Hospital Museum, 201 E).

found to have undergone sarcomatous degeneration. This case is of some pathological interest in view of the recent observations of Borrel on the supposed relation of cancerous tumours to helminthiasis.

The pancreas is said by Oser to be the seat of *secondary deposits* in more than 10 per cent. of all cases of primary carcinoma of the stomach, and, as metastasis also takes place from organs elsewhere, such as the rectum, sigmoid flexure, œsophagus, ovary, and breast, it is not uncommon. The majority of authors state that secondary carcinoma is more frequently met with than primary growth, but Hale White found only twenty-four cases with secondary deposits, as against thirty-one with a primary growth, in the Guy's Hospital post-mortem records from 1884 to 1897. Hale White, from an analysis of these records, confirms the statement of Lancereaux that the stomach is the organ from which the growth most frequently extends directly to the pancreas. Olivier and Dieckhoff are disposed to doubt some cases described as primary pancreatic, and think that their microscopical characters suggest that they may have really originated in the glands of the duodenum. Orth, however, points out that the transition of the atypical growth of intestinal gland acini into cancerous alveoli is not always easy to establish in primary tumours, and that columnar-celled carcinoma may originate in excretory ducts of the pancreas as well as in the duodenal glands. Secondary deposits of carcinoma may be found in any part of the gland, but whenever present in the pancreas are also to be found at the same time in many other organs of the body.

Secondary sarcoma of the pancreas is not uncommon. It occurs most frequently as a lymphosarcoma arising from the abdominal lymph glands, mediastinum, or duodenum. A number of cases of melanotic sarcoma have also been described. In these the primary growth is most commonly situated in the eye.

Adenoma of the pancreas may originate from the duct-epithelium, the gland acini, the islands of Langerhans, or from suprarenal rests. Examples of this condition have been described by Thierfelder, Biondi, Cesaris-Demel, Neve, and Nicholls, but in at least one of them the diagnosis is open to question. Thierfelder's case was a man who died of general tuberculosis; a definitely encapsuled but easily shelled-out tumour was found in the head of the pancreas. Biondi excised a "fibro-adenoma" from the head of the gland. Cesaris-Demel found a growth, the structure of which was similar to that of the pancreas, but its interstitial tissue, as well as that of the gland substance, was thickened. He suggests that the cirrhosis of the pancreas, developed upon a syphilitic basis, incited the formation of the tumour. Neve describes a case in which there was a glandular tumour in the region of the pancreas adherent to the duodenum and compressing the common duct. In Nicholls' case a small, encapsuled, round, somewhat flattened nodule was present on the anterior surface of the pancreas which, on microscopical examination, was found to consist of a stroma of connective tissue, arranged in the form of imperfect and irregular alveoli, that contained cells of a glandular type forming masses and wavy bands. As compared with the acinous cells, those of the tumour were smaller, their nuclei were relatively larger, and their cytoplasm was looser in texture and stained more faintly and irregularly. Nicholls concluded, from its staining reactions and structure, that the starting-point of the tumour was in an island of Langerhans.

Fig. 86.—Deposits of melanotic sarcoma in the pancreas with hæmorrhage into the gland and fat necrosis (St. Thomas' Hospital Museum, 1416).

Lymphadenoma of the pancreas is excessively rare; but two cases are referred to by Lancereaux, and Hale White speaks of the condition as having been met with at Guy's Hospital once in fourteen years, in a patient who died from Hodgkin's disease.

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CHAPTER IX

FAT NECROSIS

The term "fat-tissue necrosis" was introduced by Langerhans to describe the small, opaque, yellowish-white areas described by Balser as occurring in the inter-

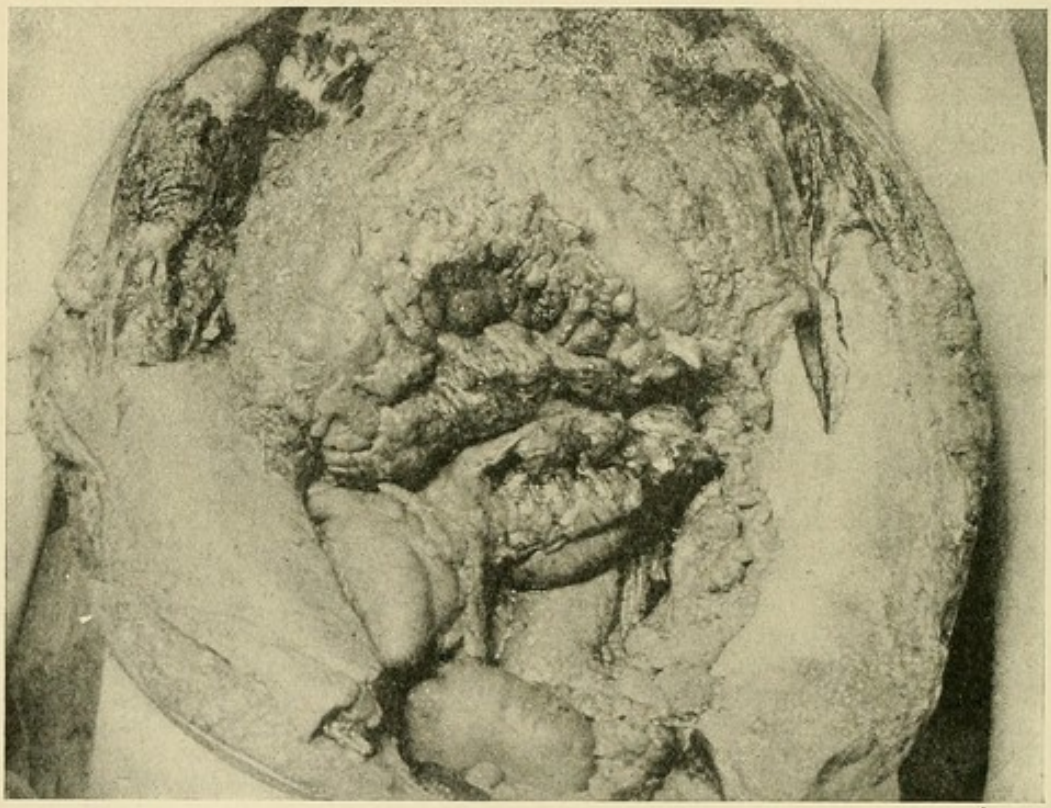

Fig. 87.—Areas of fat necrosis in the mesenteric and omental fat and in the abdominal wall in a case of acute hæmorrhagic pancreatitis (Fison).

acinous tissue of the pancreas, and more rarely in the surrounding fat, of many bodies taken indiscriminately in the post-mortem room. Balser had observed the lesion in five out of twenty-five bodies he examined, and

in two found that the process not only involved the fat about the pancreas, but was also present in scattered foci at a considerable distance from the gland. He believed that occasionally the areas might become confluent and cause death, either by their extent and the simultaneous sequestration of large portions of the abdominal fat, or from hæmorrhage, indications of which he found in the adjacent tissue, especially when the changes were extensive. Balser made microscopical preparations from the affected areas and adjacent tissues, and came to the conclusion that the lesion was due to an increase of the fat cells. Chiari confirmed the observations of Balser as to the occurrence of the condition, and stated that he had found it in five cases of severe disease of the pancreas, but did not agree as to its nature, for in his opinion the lesion was due to fatty degeneration and simple necrosis.

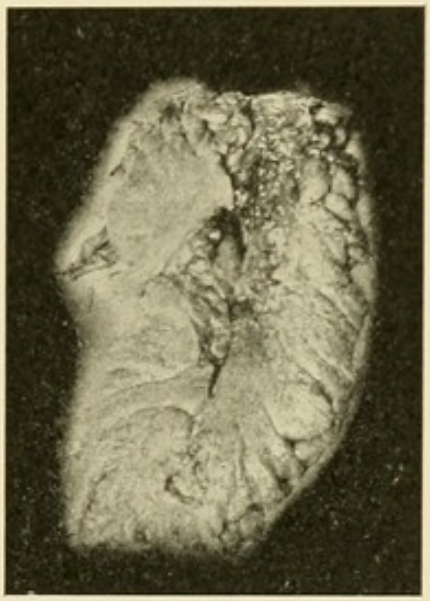

Fig. 88.—Portion of the omental fat from the same case of acute pancreatitis, showing areas of fat necrosis (Fison).

A correct explanation of the essential nature of the process was first afforded by the chemical and histological studies of Langerhans, who showed that the change of the fat cells into granular balls, and the appearance in the older foci of peculiar flakes of the size and form of ordinary fat cells, observed by Chiari, are due to splitting of the neutral fat of the cells into fatty acid and glycerine. The fatty acids are deposited as needle-like crystals within the cells, which have lost their nuclei and are necrotic, while the soluble glycerine is absorbed. Subsequently union of the fatty acids with calcium gives rise

to irregular and often globular masses of lime salts, which more or less preserve the outlines of the cells. Langerhans found that an entire lobule, or several neighbouring lobules, may form a dead mass which is separated from the living tissue by a proliferation of the fixed tissue cells, and that the dissecting inflammation is most conspicuous

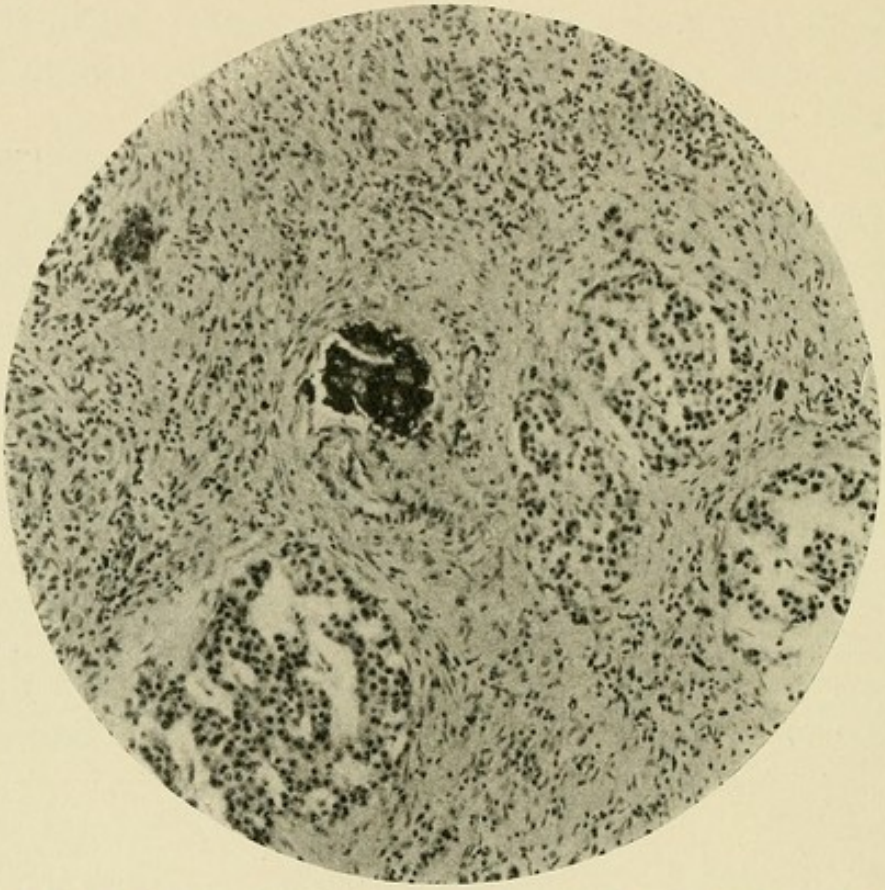

Fig. 89.—Microphotograph of fat necrosis of the body of the pancreas in a case of carcinoma of the head of the gland. General view showing normal islands of Langerhans, and a spot of fat necrosis in the centre alongside a bifurcating vessel (× 130) (Scott).

in the neighbourhood of the strands of connective tissue, although the zone of reaction is often not complete and necrotic cells are found in contact with those that are still unchanged.

Numerous instances of multiple fat necrosis have been recorded since the earlier observations of Balser and

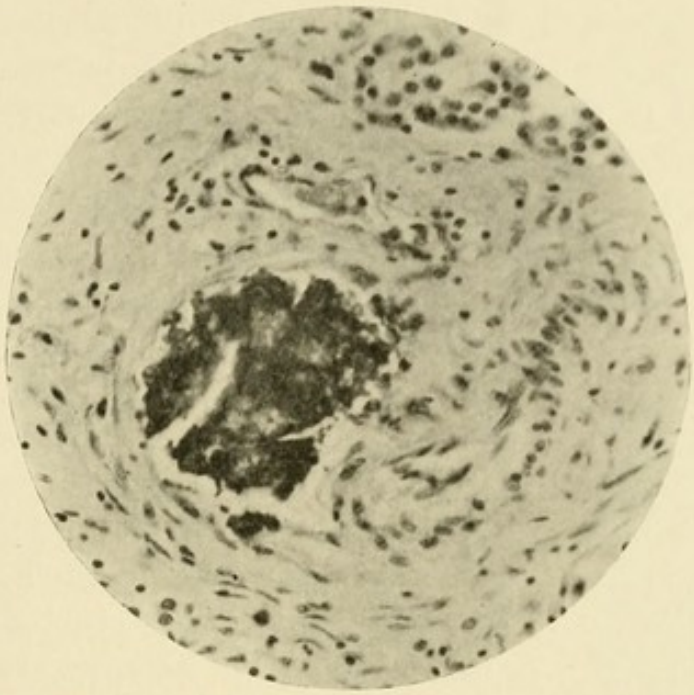

Fig. 90.—Microphotograph of fat necrosis of the body of the pancreas in a case of carcinoma of the head of the gland. The same spot of fat necrosis (× 264) (Scott).

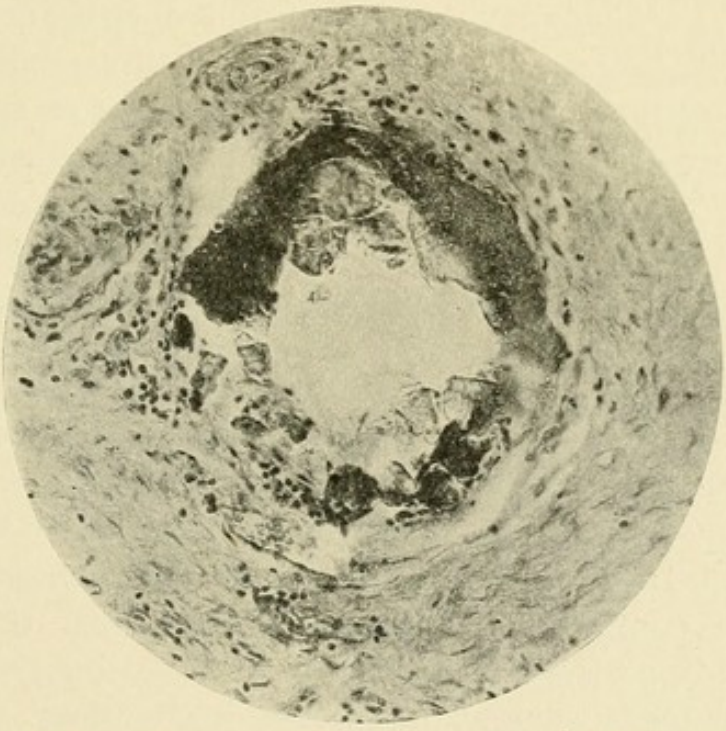

Fig. 91.—Microphotograph of fat necrosis of the body of the pancreas in a case of carcinoma of the head of the gland. Crystalline appearance in a spot of fat necrosis (× 200) (Scott).

Chiari, associated, as a rule, with well-marked structural changes in the pancreas. The lesion is usually limited to the fat of the abdomen, and is most extensive in the neighbourhood of the pancreas, but may extend to the subpleural fat, or even to the subcutaneous tissue. Foci of fat necrosis in the last situation, corresponding to reddish areas in the skin during life, have been observed by Hansemann in two cases. The condition is not confined to man, but has been found in domestic animals by Balser, Williams, Alt, Heller, and others.

Fig. 92.—Section of the body of the pancreas in a case of carcinoma of the head of the gland treated with Benda's solution, showing areas of fat necrosis (stained green), the dilated duct of Wirsung in the centre, and the splenic artery above (Leeds Path. Museum, E E 204 x).

The opaque, dull-white, or yellowish-white areas, often surrounded by a narrow hæmorrhagic zone, seen in multiple or disseminated fat necrosis are in striking contrast to the clear yellow of the surrounding normal fat, and are, as a rule, sufficiently characteristic. They may be differentiated still further by the application of a half-saturated solution of acetate of copper, as suggested by Bender, when the affected parts turn green (Fig. 92). Small areas of necrosis not visible to the naked eye may also be demonstrated by this means. The areas are of firmer consistency than the tissues in which they are situated, and hence can be felt on passing the finger over the surface. They do not, as a rule, however, project like miliary tubercles. In the neighbourhood of the pancreas they may be confluent, but elsewhere, although they may be thickly scattered, are usually seen as distinct oval or round patches, several millimetres in diameter, which in section have the shape of a split pea with the flat surface toward the peritoneum. Para-pancreatic foci, limited to

the fat within or upon the pancreas, are usually small and are easily overlooked. Although they are not so common as Balser's observations would suggest, they are not infrequently met with when carefully sought for.

The association of fat necrosis with lesions of the pancreas, and the greater severity of the changes in the neighbourhood of the gland, early suggested that the two were in some way connected. Balser, Langerhans, Seitz and Fraenkel considered that fat necrosis was the cause of the inflammation, hæmorrhage, and necrosis of the pancreas with which it often occurred. Ponfick thought that it merely predisposed the tissues to inflammatory and other changes. Dieckhoff believed that, although fat necrosis may give rise to diseases of an inflammatory nature, it is possible that the same cause which occasions the inflammation may also cause fat necrosis. Lindsay Steven admitted that extensive fat necrosis might lead to necrosis of the pancreas, but considered that the two processes were usually independent. Fitz, and subsequently Körte, maintained, however, that fat necrosis was the result of pathological processes affecting the pancreas, and this is the explanation that is now generally accepted.

Some observers, including Balser, have sought to connect fat necrosis with a bacterial invasion, and have succeeded in finding a variety of micro-organisms in the affected parts. Jackson and Ernst, in a case of suppurative pancreatitis with fat necrosis reported by Fitz, isolated four different types of bacteria. Ponfick cultivated a bacillus which he thought was allied to bacillus coli communis, and Welch also identified bacillus coli in a case of hæmorrhagic pancreatitis with fat necrosis. Other investigators have obtained similar results, but Fraenkel, on the other hand, in spite of most careful microscopical and cultural investigations, was unable to find any evidence of bacterial infection. More recently

Sawyer has made cultures from the necrotic patches in a case of fat necrosis and found that they were sterile, and microscopical sections in other cases also failed to shew any micro-organisms. The explanation of the discordant results obtained by different observers is no doubt that offered by Hlava, Fitz, Leonhard, and Welch, who consider that the presence of micro-organisms is due to a secondary invasion and takes no part in the production of the lesion.

Experimental work on the production of fat necrosis was first undertaken by Langerhans. He injected an infusion, made by grinding up the pancreas of a freshly killed rabbit with finely splintered glass, into rabbits and dogs, and succeeded, in one of thirteen experiments, in producing a small opaque focus at the site of injection, which had the histological characters of fat necrosis. He consequently concluded that it was possible to produce fat necrosis by the action of fresh pancreatic juice upon living fat tissue. Jung attempted to reproduce the condition by introducing gelatin capsules containing pancreatic extracts, and pieces of fresh pancreas from another animal, into the abdominal cavities of rabbits. Three experiments gave doubtful results, as peritonitis followed, but well-marked areas of fat necrosis were produced in one instance. Under the direction of Hildebrand, a series of investigations were undertaken by Dettmer. Fat necrosis about the distal portion of the pancreas was found to be produced by constricting it with a ligature, and was more abundant when the veins of the ligatured part were tied to prevent possible absorption by the blood-vessels of the obstructed secretion. Similar lesions in the neighbourhood of the gland were also produced by cutting it across transversely and allowing the pancreatic juice to flow directly into the abdominal cavity. Injections of trypsin gave rise to no fat necrosis, so that it was probable that the condition was not due to the

proteolytic but to the fat-splitting ferment of the pancreatic juice. Körte obtained similar experimental results and concluded that fat-tissue necrosis may be produced experimentally by injuries and inflammations of the gland, especially by solution of continuity and the implantation of excised pieces. The experiments of Flexner, Williams, and Milisch, conducted on lines similar to those of Dettmar and Hildebrand, also confirmed the observations made by those investigators. Oser produced foci of fat necrosis about the pancreas, and in the omentum, by ligaturing all the blood-vessels of the organ and separating it from the duodenum, thus entirely depriving it of its blood supply. Hæmorrhagic infiltration of the parenchyma, and fat necrosis in the neighbourhood of injured tissue, were found by Blume to result from complete obstruction of the circulation of a portion of the gland for so short a time as twenty minutes. As the result of a large number of experiments in which they ligatured the pancreas, and tied or cut the ducts, Katz and Winkler came to the conclusion that fat necrosis is produced by the fat-splitting ferment of the pancreatic juice, but that its activity is particularly developed in those situations where the resistance of the parts has been lowered by obstruction of the circulation or infiltration with blood.

In most of the experiments already referred to the production of fat necrosis had been confined to the abdominal fat, and usually to that in the immediate neighbourhood of the pancreas. Opie, however, in a series of experiments he undertook succeeded in reproducing the more widely spread condition occasionally observed in man, and showed that the same cause is responsible for it as for the local lesions. He found, as previous observers had done, that ligature of the pancreatic ducts does not always give rise to fat necrosis, even when the animal survives the operation for three weeks or more, but in six experiments he succeeded in bringing about changes

which in two instances extended to the subcutaneous and pericardial fat, besides involving that of the abdomen, and in other four affected the omental and mesenteric fat. The extent and intensity of the lesion appeared to depend

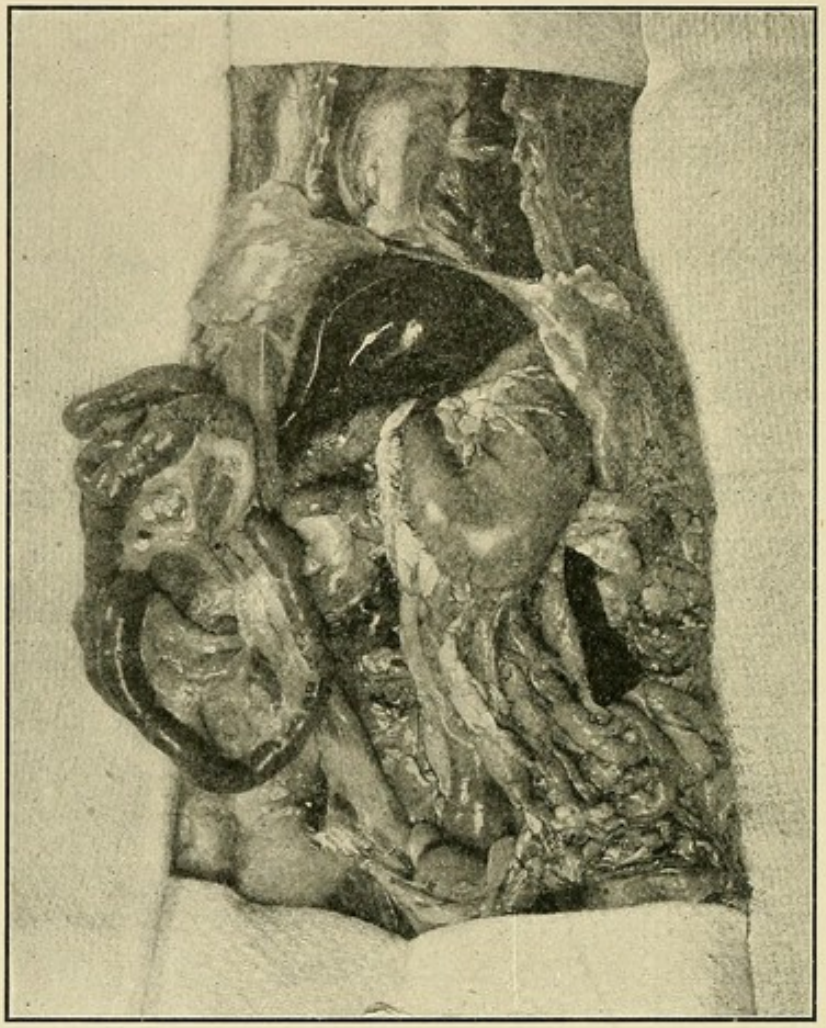

Fig. 93.—Experimental fat necrosis: Administration of pilocarpin after ligation of pancreatic ducts. Foci of necrosis in omental and mesenteric fat, in fat below parietal peritoneum, and in fat of parietal pericardium (Opie).

upon the time the animal survived the operation of ligating, or tying and cutting, the pancreatic ducts, for when death took place in twenty to twenty-five days the necrosis was more extensive than when the animal lived a shorter time. Opie assumed that this might be

due to the condition being produced by a gradual diffusion of the pancreatic juice, and that, if the activity of the gland could be stimulated, fat necrosis in distant parts would more readily take place. Making use of the observation of Heidenhain, Gottlieb, and others that the pancreatic secretion is increased by pilocarpin, he administered that drug to a cat, after tying the pancreatic ducts, and, at the end of four days, found that there was local necrosis of the omental, mesenteric, retroperitoneal, intermuscular, and pericardial fat, whereas in a control animal, to which no pilocarpin had been given, there were, in the same time, only small foci of necrosis in the neighbourhood of the pancreas.

Milisch, as the result of his experiments, came to the conclusion that fat necrosis may be caused by an escape of pancreatic juice into the abdominal cavity, and although this is no doubt the correct explanation in a few cases in which a ruptured duct is found opening directly into a peritoneal cavity, it is probably not true for the majority. Opie points out that in the experiments he performed an escape of the confined secretion into the peritoneal sac was not likely, for the cut ends of the ducts were found to be surrounded by adhesions, and the condition of the parts pointed to penetration having taken place into the tissues about the organ, while the distribution of the lesion, which was most intense near the pancreas and in the structures anatomically continuous with it, was against its having arisen from a flow of pancreatic juice over the surface of the peritoneum. In order to test the ability of the pancreatic secretion to produce fat necrosis, when directly injected into fat tissue, Opie arranged an experiment in which the cut ends of the pancreatic ducts were made to lie in the subcutaneous tissue of the abdominal wall. In an animal which survived the operation twenty-seven days, he found that areas of fat necrosis were present in the sub-

cutaneous tissue of the abdomen and thorax, extending in places almost as far as the vertebral column, but were most abundant in the neighbourhood where the cut ends of the ducts terminated. Small areas were also found in the omentum, between the pancreas and the spleen, and in the subperitoneal tissue around the operation wound, but none could be found in the duodenal mesentery, and mesentery of the large intestine, where previous experiments had shown fat necrosis from simple ligature of the ducts to be most abundant.

In a total of twenty-five cases of acute necrosis of the pancreas in dogs, produced by various methods, Gulcke found fat necrosis in all but one. This animal died within eight hours, possibly before there was time for fat necrosis to occur. In most instances the lesion was widely spread through the abdominal cavity, and in two animals was also found in the mediastinum and pericardium, where it followed the course of the lymph-vessels. In six dogs the pancreas was walled off by tampons from the remainder of the peritoneal cavity, either at the time of the operation or a few hours later. In none of these was there any fat necrosis of the general cavity, although it occurred along the drainage tract and in the superficial fat. Gulcke is of opinion that these experiments prove that fat necrosis is produced secondarily as the result of a primary necrosis of the pancreas with direct diffusion, or absorption, or transportation of the pancreatic secretion through the lymph-vessels.

Hildebrand has suggested that obstruction to the venous circulation, by preventing the absorption of the pancreatic secretion by the blood, might favour fat necrosis, but Opie maintains that in his experiments no disturbance of the circulation took place, and it can therefore play but a small part in the process. The absence of hæmorrhagic infiltration and local ischæmia in his experiments shows, Opie thinks, that they are not essential

for the production of fat necrosis, in spite of the views of Katz and Winkler to the contrary.

It has already been pointed out in a previous section that ligature of the pancreatic ducts in animals gives rise to chronic interstitial inflammation, and it might therefore be inferred that the fat necrosis produced by preventing the flow of secretion in this way is connected with the change of structure. Opie maintains, however, that it is not an essential factor, for the lesion was found in an animal that survived the operation but twenty-four hours, and was also widely disseminated in another which lived only four days after ligature of the ducts and the subsequent injection of pilocarpin.

When speaking of the pathology of acute pancreatitis we mentioned that not infrequently fat necrosis was found to accompany the pancreatic lesion produced by injecting various irritating and toxic substances into the parenchyma and ducts of the gland. The experiments of Hlava, Oser, and Flexner are particularly noteworthy in this connection, for they found that injections of dilute acid, dilute alkalies, artificial gastric juice, turpentine, or suspensions of bacteria, while causing more or less serious injury to the parenchyma, are liable to be accompanied by necrotic changes in the pancreatic and abdominal fat.

Langerhans, Dettmer, Hildebrand, Katz, and Winkler inferred, from their observations and experiments, that the constituent of the pancreatic secretion to which fat necrosis was due was the fat-splitting ferment, but the demonstration of its presence in the necrotic foci was first made by Flexner. He showed that when pieces of the altered tissue from human and experimental cases were allowed to act upon neutral butter-fat, fatty acids, which could be recognized by their reaction and odour, were set free. Opie has since repeated the experiment with portions of necrotic fat from the omentum, mesen-

tery, subcutaneous tissue, and pericardium in two animals in which fat necrosis had been produced by ligature of the ducts, and obtained a well-marked reaction in each instance.

Clinically disseminated fat necrosis has been found to be associated, as a rule, with some well-marked lesion of the pancreas. In most cases there has been a hæmorrhagic infiltration of the gland, accompanied by more or less degeneration and necrosis of the parenchyma. Gangrenous pancreatitis is found somewhat less frequently, but sequestration of the gland may arise, as Langerhans suggests, from extensive necrosis of the surrounding fat. Suppurative inflammation is occasionally accompanied by fat necrosis, and chronic interstitial inflammation, whether due to blocking of the ducts or some other cause, is at times found in association with necrotic changes in the interstitial and surrounding fat tissue of the organ. Carcinoma of the head of the pancreas has been found with focal fat necrosis in some cases.

It has been usually said that the presence of extensive fat necrosis is a fatal sign, but that it is not always so, is shown by the complete recovery of a case of acute pancreatitis with well-marked disseminated necrosis that was operated on by one of us. Körte has also met with the condition during life and found that after a time it had disappeared, but in his cases there had been no evident disease of the gland. Slight changes are not infrequently seen in the pancreas and neighbouring peritoneal fat post-mortem without any marked alteration in the structure of the organ, and without there having been any symptoms during life. In these cases the diffusion of pancreatic juice is probably either agonal or post-mortem. Cases have been reported by Fraenkel and Flexner, however, in which there was disseminated fat necrosis, but no demonstrable lesion of the pancreas, and to which this explanation would not apply. A case of

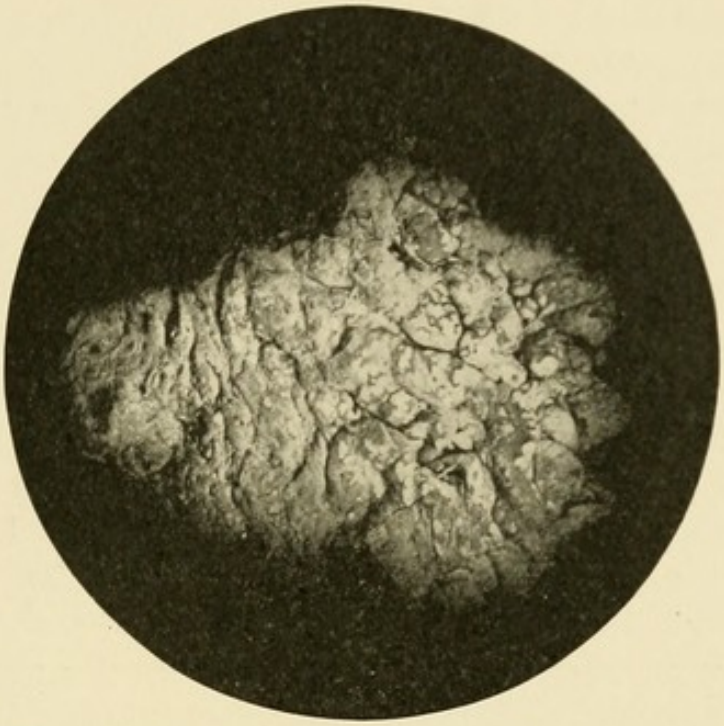

Fig. 94.—Fat necrosis of the omentum in a case of chronic interstitial pancreatitis (Santos).

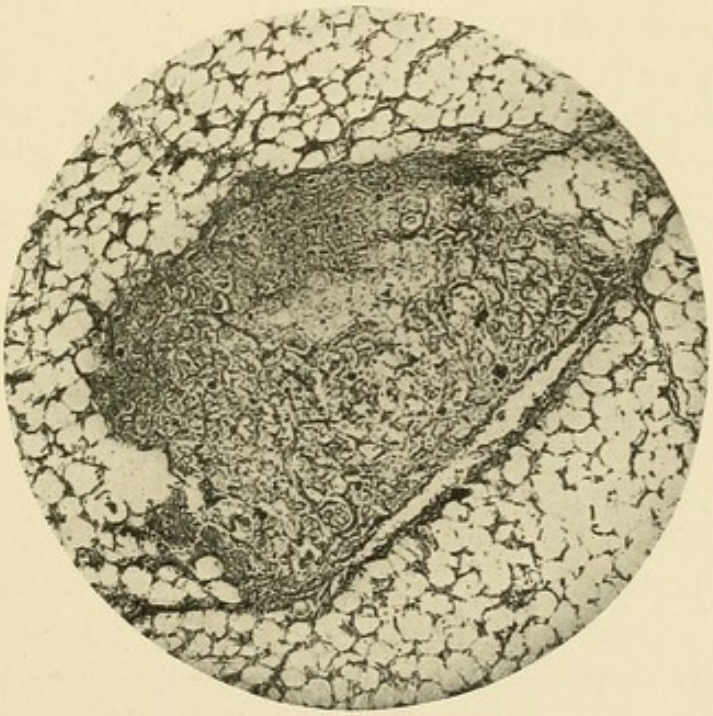

Fig. 95.—Microphotograph of an area of fat necrosis in the same case of chronic pancreatitis (Santos).

acute peritonitis with fat necrosis, unaccompanied by any discoverable disease of the pancreas, has been recently reported by Fawcett to the Clinical Society of London, and Sawyer has published details of eight cases of fat necrosis, in two of which there was no obvious pancreatic lesion. In the first of Sawyer's cases, death followed hydrochloric acid poisoning, and post-mortem there were large areas of fat necrosis on the surface of the pancreas and in its substance. There was no necrosis, however, beyond the region of the pancreas. The gland itself "seemed to be normal in size and showed the usual lobulation." Microscopically too it "appeared normal." The pancreatic duct was, however, obstructed by inflammatory changes, and the duodenum, and the first twelve inches of the jejunum, were acutely inflamed. Sawyer attributes the fat necrosis in this case to damage or injury of the pancreas by the corrosive poison, but, in the light of Opie's experiments, it appears not improbable that stimulation of the pancreas by secretin, set free from the intestinal mucous membrane through the action of the hydrochloric acid, may have contributed, or even brought about, the result, especially as there was some obstruction of the duct. In the second case the condition was found in association with mitral stenosis, with infarcts of the kidneys and spleen, many of which were recent. The fat necrosis chiefly affected the surface and substance of the pancreas, but a few points were also found in the root of the mesentery. Microscopically a few small areas of necrosis of the gland tissue were found which Sawyer thinks may have arisen from multiple emboli, although no thrombosis of the vessels could be demonstrated. To the setting free of the fat-splitting ferment from these areas he attributes the fat necrosis, but it is also noted that the patient was slightly jaundiced, suggesting that there may have been some catarrhal pancreatitis.

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CHAPTER X

CHEMICAL PATHOLOGY

The chemical changes induced in the body by diseases of the pancreas may be considered under two headings: first, those which are connected with the processes of digestion; and, secondly, those which result from disturbances of internal metabolism and are shown by alterations in the blood, urine, etc. No hard and fast line can be drawn, however, between the two, and, as we shall see later, disturbances of digestion are liable to affect the internal economy of the body, not only through the direct effects they exert upon nutrition, but also by the formation of various toxic substances, which, being absorbed from the intestine, give rise to alterations in the blood and other tissues, and also produce changes in the urine.

The most important digestive disturbances, due to disease of the pancreas, arise from *absence or diminution of its secretion.* Obstruction of the pancreatic duct, from the pressure of tumours, or from calculi in the common bile-duct, or in the pancreatic ducts themselves, is the commonest condition to give rise to more or less complete absence of the secretion from the intestine, but atrophy, fatty degeneration, or sclerosis of the gland may occasionally advance so far as to destroy practically the whole of the secreting parenchyma.

In less advanced cases the secretion may be impaired, and in these, and in inflammatory lesions arising from whatever cause, the secretory activity is diminished, to a degree corresponding to the extent and intensity of the lesion. Among the commonest causes of impaired secre-

tion are acute and chronic catarrhs of the duodenum, often combined with gastritis, general enteritis, and colitis. These may directly affect the secretion by giving rise to a catarrhal pancreatitis, but may also indirectly exert an action on the digestive processes by interfering with the supply of enterokinase by which the proteolytic ferment of the pancreas is activated under normal conditions. Temporary checking of the secretion, or a chronic diminution in the amount, is said by Herter to occur in prostrating illnesses and from fever, anæmia, extreme nervous exhaustion, fright, grief, mental overwork, worry, and excessive muscular or sexual fatigue. Stolnikow, investigating the condition of the secretion in fever, found that it was diminished, and finally ceased, although the gland itself was never quite free from ferment.

Little is known concerning *excessive pancreatic secretion.* The flow of pancreatic juice and that of saliva are known to be both stimulated by the administration of pilocarpin. Fats also favour the formation and secretion of pancreatic juice, and, as we have seen, the gland is powerfully stimulated by the presence of hydrochloric acid in the upper part of the small intestine, so that in hyperchlorhydria it is possible that a quantity in excess of the requirements of the food may be secreted. It is also possible that in the early stages of the inflammatory lesions of the gland there may be an increased flow of secretion, corresponding to the salivation that occurs in inflammatory affections of the salivary glands.

Starling has proved that a mixture of pancreatic juice and intestinal secretion has an extraordinarily powerful action on the walls of the bowel, producing inflammation and erosions, so that it is not unlikely that an excessive secretion may give rise to a more or less marked enteritis, with consequent diarrhœa. Senn has suggested that there is a causal relationship between the profuse diar-

rhœa, seen at times with cysts and degenerations of the pancreas, and the glandular changes.

The digestive disturbances likely to result from *absence or a diminution of the secretion* may be inferred from a knowledge of its physiological functions. Since it is the most important of all the digestive fluids, and exerts an action upon each of the three principal classes of food material, any interference with its activities may be expected to lead to defective assimilation of fats, proteids, and carbohydrates, and an examination of the fæces should show that an abnormally high proportion of the food is passed in an undigested state.

The preparation of fats for absorption by the intestine is peculiarly a function of the pancreatic juice, and it is to the investigation of undigested fat in the stools in lesions of the pancreas that the attention of experimentalists and clinicians has therefore been chiefly devoted. Claude Bernard pointed out that, when the pancreas was destroyed by injecting oil into the main duct, an abnormal amount of fat was present in the fæces, often in such quantities as to coat them with an oily covering, and while his results were confirmed by some observers, they were contradicted by others, who subsequently carried out similar investigations.

A series of careful experiments upon dogs carried out by Abelmann, under the direction of Minkowski, were the first to really place the matter on a sure footing, and to clearly demonstrate that when the pancreatic secretion is prevented from entering the intestine, or is diminished in amount, by complete or partial extirpation of the gland, the digestion and absorption of fat contained in the food are more or less seriously interfered with. He found that when the pancreas was entirely removed, non-emulsified fat was not absorbed at all, and emulsified fat only to a slight extent (18.5 per cent.). Animals from which the pancreas had been partly removed showed better

absorptive powers, but their capacity in this direction was limited, for whereas small amounts of emulsified fats were about half absorbed, larger amounts, 70 to 150 grams, were less efficiently dealt with. A natural emulsion of fat in the form of milk was much more completely utilised in both instances, 30 per cent. of large amounts and 53 per cent. of smaller quantities being absorbed when the pancreas had been completely extirpated, and up to 80 per cent. when portions of the gland had been left behind. The administration of pig's pancreas with the food was found to facilitate the absorption of fats, and pointed to the absence of the pancreatic secretion being the main cause of their defective assimilation. Abelmann consequently concluded that all fats, with the exception of milk, unquestionably need the influence of the pancreas for their utilization. Sandmeyer in his experiments obtained similar but less consistent results. He also found that the absorption of fat was increased by the addition of fresh pancreas to the food. After extirpating the pancreas in a dog Cavazzani found that unused fat was present in the fæces, and that, while the animal ate soap with great eagerness, it rejected fat. Baldi observed a large amount of oily fat, which did not solidify at the temperature of the room, in the fæces of depancreatised dogs fed on meat from which the fat had been removed, but was unable to produce so high a degree of steatorrhœa by tying the bile-duct. Rosenberg produced atrophy of the pancreas by tying the vessels and cutting the duct; he then found that the fæces were bulky, clay-coloured, and contained a large amount of fat.

These experiments show that in animals extirpation, or destruction of the pancreas is attended by a defective absorption of fat, except that of milk, and that while similar but less marked effects can be produced by excluding bile from the intestine, the increased proportion of fat

in the stools is to be mainly attributed to absence of the pancreatic secretion.

Analysis of the fæces in Abelmann's experiments showed that from 30 to 85 per cent. of the non-emulsified fat had undergone cleavage into fatty acids and soaps. He concluded therefore that, after total extirpation, fat cleavage was not disturbed. Katz, however, investigating the condition of the fæces in a dog operated on by Oser, found that there was "a surprising diminution" in the cleavage of fat, after partial extirpation of the pancreas and tying the main excretory duct, 51.53 per cent. being neutral fat, 46.04 per cent. fatty acid, and 2.33 per cent. soaps.

Opportunities of investigating the effects of simple and complete exclusion of the pancreatic secretion from the intestine in man are rare, for total degeneration of the secreting parenchyma is exceptional, and when the duct of Wirsung is blocked the results of an associated biliary obstruction that usually occurs have also to be taken into account. Most of the published observations therefore relate to cases in which the digestive functions of the pancreas have been more or less interfered with, but yet not completely abolished, and in some the results have been complicated by a simultaneous interference with the flow of bile into the intestine. The majority of authors have been satisfied with a naked-eye description of the fæces, and although the more striking variations from the normal can be recognized in this way, it gives no precise data on which to base an opinion as to frequency of an excess of fat in the stools in disease of the pancreas, and furnishes no criterion by which the fat contents can be compared in different lesions of the gland, or with that in the dejecta in other disorders. Ziehl, in 1883, published an account of a case of carcinoma of the pancreas, with jaundice, in which he found that about 50 per cent. of the dried fæces consisted of fat. Demme

investigated the stools from a case of congenital syphilis with jaundice, gummata of the liver, and atrophy of the pancreas, and found from 64 per cent. to 73.3 per cent. of fat. Weintraud's patient lost in the fæces from 22 to 25 per cent. of the fat taken as food, a considerable excess over the 7 to 11 per cent. normally undigested, and in Deucher's two patients the loss was still more marked, being 52.8 per cent. and 83 per cent. respectively. In a case of cancer of the pancreas in which the fæces were examined over a month before the onset of jaundice, Oser found that 45.9 per cent. of the dry weight consisted of fat, and that this was almost entirely neutral fat. Numerous fat-needles and fat-drops were seen microscopically. On the other hand, Müller was not able to detect any increase of fat, either macroscopically, microscopically, or chemically, in the cases of obliteration and cystic degeneration of the pancreas that he investigated. He attributed the steatorrhœa in such cases entirely to the absence of bile, and stated that when bile was excluded from the intestine from 55.2 to 75.5 per cent. of the fat contained in food was passed unabsorbed, as against the normal 7 to 11 per cent. The same observer, investigating three cases of obstruction of the duct of Wirsung, with degeneration of the gland, found that, although the total quantity of fat absorbed was not far from the normal, the cleavage of fats in the intestine was very considerably diminished, for only 39.8 per cent. of the fat in the fæces was found to be split into fatty acids and soaps, instead of the normal of about 84 per cent.

Our own observations on the *fat contents of the fæces in diseases of the pancreas* have been mainly carried out by a special method, described by one of us at the Leicester meeting of the British Medical Association in 1905. This, while much more rapid than the Soxhlet process, gives results that are satisfactory for clinical work and for purposes of comparison. It is carried out as follows:

Two clean, dry, Schmidt-Stokes milk-tubes, labelled A and B, and provided with a 10 c.c.-mark, are taken, and into the lower bulb of each is introduced an accurately weighed quantity (about half a gram) of the finely powdered fæces, that have been dried to a constant weight on a water-bath. The residue on the watch-glass used for weighing, and on the sides of the short-necked funnel with which the powder is introduced into the tube, is washed down with a fine jet from a wash-bottle, which for the A-tube contains hydrochloric acid (1:3), and for the B-tube plain water. The sides of the tube are also washed until the whole of the sample is collected in the lower bulb, and the 10 c.c-mark is reached. The A-tube is then heated in boiling water for twenty minutes, occasionally rotating it so as to well mix the contents. After cooling, both tubes are filled to the 50 c.c.-mark with ether, securely corked, and inverted forty times, taking care that the whole of the solid material runs through at each turn. Each tube is then rotated between the hands, and allowed to stand for half an hour or more, in order that the solid residue may be collected into the lower bulb. Considerable care is necessary in carrying out this part of the process in some instances, or a perfectly clear supernatant layer of ether, free from solid particles, is not secured. With a pipette, exactly 20 c.c of the clear ethereal extract are drawn off from each tube and delivered into two CO_2-flasks of known weight, the amount of ether left in the tubes being noted. The ether in the flasks is then evaporated, the residue dried on the water-bath, and the flasks again weighed. From the amount of extract yielded by 20 c.c. of ether, and the quantity of ether left in the tubes, the total amount yielded by the weight of dried fæces used may be calculated, and from this the percentage in the stool determined.

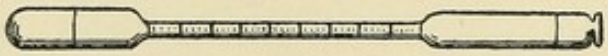

Fig. 96.—Schmidt-Stokes milk-tube.

The result from the A-tube gives the total fat in the fæces, including the neutral fats, free fatty acids, and combined fatty acids, or soaps, since the latter will have been decomposed by being boiled with the hydrochloric acid and thus rendered soluble; that from the B-tube represents the neutral fats and fatty acids only, as the soaps will remain undissolved by the ether: the difference between the two will therefore give the proportion of saponified fat present. Other substances in the fæces soluble in ether, such as cholesterin, lecithin, cholic acid, and pigments, are included in the estimates, but as the quantity is small it does not appreciably affect the results. For convenience of reference we shall speak of the yield from the A-tube as "total fat," that from the B-tube as "neutral fat," and the difference between the two as "fatty acid."

The solid residue from the B-tube can be used for the detection of stercobilin. For this purpose it is filtered off, extracted with acid alcohol, the extract neutralised with ammonia, and mixed with an equal quantity of 10 per cent. zinc acetate in alcohol. The precipitate that forms is removed by filtration, and the clear filtrate examined with a lens, against a black background, for the green fluorescence that indicates the presence of stercobilin. The intensity of the colour varies with the amount of pigment, so that by always using approximately the same proportion of fæces and of the reagents any marked variation from the normal can be detected.

We have examined over three hundred specimens of fæces by these methods, but taking a consecutive series of one hundred recent cases, in which it has been possible to determine the condition of the pancreas and biliary passages at operation or post-mortem, and comparing the results with those obtained in sixteen normal specimens, they may be classified as follows:

ANALYSIS OF THE FÆCES IN ONE HUNDRED CASES OF SUSPECTED DISEASE OF THE PANCREAS.

	No.	Reaction.	Stercobilin.	Colour.	Organic Matter.	"Total Fat."	"Neutral Fat."	"Fatty Acid."	Organic Matter not Fat.	Muscle Fibres.	Ash.
I. Chronic pancreatitis with obstruction: Jaundice	18	Acid.....14 Neutral .. 3 Alkaline .11	Present ..12 Traces... 6 Nil 0	White . 6 Yellow.10 Brown. 2	89% (91 to 86%)	53% (82 to 26%)	38% (37 to 20%)	15% (46 to 4%)	26% (56 to 8%)	4	11% (14 to 8%)
No jaundice	5	Acid..... 4 Neutral .. 1 Alkaline . 0	Present .. 5 Traces... 0 Nil 0	White.. 0 Yellow. 3 Brown. 2	87% (93 to 79%)	49% (76 to 17%)	38% (70 to 6%)	11% (26 to 3%)	38% (26 to 3%)	3	12% (20 to 7%)
II. Chronic pancreatitis, no obstruction: Jaundice	6	Acid..... 3 Neutral .. 2 Alkaline . 1	Present .. 5 Traces... 1 Nil 0	White . 2 Yellow. 3 Brown. 1	89% (92 to 83%)	60% (82 to 33%)	36% (65 to 14%)	24% (67 to 1%)	29% (34 to 2%)	1	11% (16 to 7%)
No jaundice	27	Acid.....15 Neutral . 9 Alkaline . 3	Present ..27 Traces... 0 Nil 0	White . 0 Yellow.12 Brown.15	87% (92 to 85%)	34% (66 to 10%)	21% (51 to 5%)	13% (25 to 4%)	53% (81 to 21%)	8	12% (20 to 8%)
III. No pancreatitis, stone in gall-bladder or common duct: Jaundice	8	Acid..... 0 Neutral .. 3 Alkaline . 5	Present .. 5 Traces... 3 Nil 0	White . 2 Yellow. 5 Brown. 1	86% (98 to 83%)	55% (72 to 24%)	19% (46 to 5%)	36% (46 to 16%)	31% (78 to 16%)	1	13% (17 to 10%)
No jaundice	12	Acid..... 1 Neutral .. 2 Alkaline . 9	Present ..12 Traces... 0 Nil 0	White . 0 Yellow. 5 Brown. 7	84% (86 to 80%)	39% (66 to 16%)	18% (23 to 7%)	21% (43 to 8%)	45% (70 to 15%)	2	15% (19 to 13%)
IV. Malignant disease of the pancreas: Jaundice	24	Acid.....22 Neutral .. 1 Alkaline . 1	Present .. 1 Traces... 2 Nil 22	White .22 Yellow. 2 Brown. 0	89% (94 to 85%)	77% (93 to 40%)	50% (69 to 31%)	27% (36 to 3%)	12% (38 to 1%)	20	10% (13 to 7%)
V. Normal	16	Acid.....16 Neutral .. 0 Alkaline .. 0	Present ..16 Traces... 0 Nil 0	White . 0 Yellow. 3 Brown.13	85% (86 to 76%)	21% (27 to 8%)	11% (21 to 5%)	10% (19 to 4%)	62% (76 to 43%)	2	12% (16 to 9%)

It will be seen that the percentage of "total fat" in the fæces has, as a rule, been in excess of the normal in those cases in which there was reason to believe that there was a lesion of the pancreas. In one case of malignant disease of the head of the gland as much as 93 per cent. was found to be present, and in no instance has it fallen below 40 per cent., the average amount being 77 per cent. Chronic pancreatitis, associated with obstruction of the common bile-duct, appears in severe cases to interfere almost as much with the fat digestion as malignant disease, for 82 per cent. was found in one instance, where there was jaundice, and 76 per cent. in another, where there was no discolouration of the skin and bile-pigment was absent from the urine. That the high proportion of fat met with in some of these cases is not entirely due to the biliary obstruction is shown by the fact that as great an excess has been met with in others in which no obstruction to the free flow of bile into the intestine was present. Simple biliary obstruction, not associated with pancreatic disease, may, however, cause a very considerable increase of fat in the stools, so that in those cases where there is both obstruction of the common bile-duct and disease of the pancreas both probably influence the result. Although severe or wide-spread inflammation of the pancreas would appear to always give rise to a certain amount of steatorrhœa, we have repeatedly met with cases of pancreatitis in which the proportion of fat in the fæces was normal, or even subnormal, but these have been of a mild type and generally in an early stage where the head of the gland only was involved.

On comparing the proportions of "neutral fat" and "fatty acid," as indicating the degree to which the process of saponification has been carried in the intestine, we see that in simple pancreatitis, not associated with jaundice, the former was usually much in excess of the latter, whereas in cases of biliary obstruction, not accom-

panied by pancreatic changes, the reverse was generally found. The effect produced by the coexistence of pancreatic disease and biliary obstruction would appear to depend upon the relative extent and standing of the two conditions, for whereas in malignant disease of the head of the pancreas the "neutral fat" has always been in excess of the "fatty acid," the latter in some cases of recent pancreatitis with gall-stone obstruction has been found to preponderate. It must be remembered, however, that even the total absence of pancreatic juice and bile does not necessarily put an end to the fat-splitting process in the intestine, for, under the influence of organisms of the colon group, the conversion of fats into glycerine and fatty acids may go on energetically in the lower part of the small intestine, but since the absorption of these products will be interfered with by the absence of bile and the situation in which the process takes place, they will be excreted to a large extent in the fæces. The presence of a higher proportion of saponified fat in the stools in some cases of malignant disease and serious pancreatitis than might at first sight be expected is probably to be explained, at least in part, in this way.

The different results obtained on examining the fæces in apparently similar cases is shown by a series of analyses we have recently had the opportunity of making in two instances of pancreatic disease associated with biliary fistulæ. The second also illustrates the beneficial effects that may be produced by suitable treatment even in advanced and serious cases of pancreatitis. In the first case the biliary fistula formed after an operation for gall-stones undertaken by another surgeon, for whom an examination of the urine and fæces had been made for diagnostic purposes by one of us. The fæces were then found to be neutral in reaction, of a light brown colour, and to contain a fair amount of stercobilin. Chemical examination showed:

Organic matter	84.7%
Total fat	41.9%
Neutral fat	26.4%
Fatty acid	15.5%
Organic matter not fat	42.8%
Inorganic ash	15.3%

On a second examination being made six months later, no stercobilin could be found in the fæces, they were alkaline in reaction, and of a greasy white appearance. Chemical analysis showed:

Organic matter	85.8%
Total fat	85.5%
Neutral fat	35.6%
Fatty acid	49.9%
Organic matter not fat	0.3%
Inorganic ash	14.2%

An increase of 34.4 per cent. in the "fatty acid" as compared with 9.2 per cent. in the "neutral" fat.

In the second case the patient had a biliary fistula when he came under our observation. The fæces were white and shining, acid in reaction, and contained only a faint trace of stercobilin. Microscopically crowds of fat globules, fat crystals, and undigested muscle fibres were found. Chemical examination gave the following results:

Organic matter	93.0%
Total fat	72.6%
Neutral fat	69.7%
Fatty acid	2.9%
Organic matter not fat	20.4%
Inorganic ash	7.0%

A fortnight after this examination had been made he was operated on by one of us and a cholecytenterostomy performed. No gall-stones were found at the time of operation, but the pancreas was dense, hard, and rugged, and closely gripped the common bile-duct, which passed through it. Examination of the fæces a month later, when the patient had returned to a normal mixed diet, showed that they were of a light yellow, almost white, colour, acid in reaction, and contained many fat globules,

fat crystals, and some undigested muscle fibre. Chemically the following results were obtained:

Organic matter	93.1%
Total fat	68.2%
Neutral fat	65.7%
Fatty acid	2.5 %
Organic matter not fat	24.9%
Inorganic ash	6.9%

The patient was then placed upon "pancreon," and it was found, when the fæces were examined five months subsequently, that they were still of a light colour, although they contained a normal amount of stercobilin, the reaction was acid, and microscopically a few fat globules, fat crystals, and some muscle fibres were present. The chemical analysis gave:

Organic matter	93.2%
Total fat	40.2%
Neutral fat	26.1%
Fatty acid	14.1%
Organic matter not fat	53.0%
Inorganic ash	6.8%

Turning the bile into the intestine thus produced practically no change in the fat content of the fæces, but when the deficiency of pancreatic juice was partly supplied by the administration of "pancreon" the neutral fat was diminished over 40 per cent. and the fatty acid increased 11 per cent., while the amount of unabsorbed fat in the stools was also very considerably diminished.

In most of our investigations on the fæces in pancreatic disease the patients have been upon an ordinary mixed diet, and, for purposes of clinical diagnosis, we have found that this is quite sufficient, and that it is not necessary to delay the examination of the stools until a uniform fixed standard of diet has been established. It is necessary, however, that the character and amount of the food should be borne in mind when the results of the chemical analysis are considered, for some fats are more readily absorbed than others, and large quantities might

pass through the intestine unchanged even in normal persons. We have already mentioned that experimental investigations on depancreatised animals have proved that a natural emulsion, such as milk, is more readily dealt with than fats in the solid form, and there is evidence which shows that the chemical constitution of the latter is also not without influence upon their susceptibility to digestive processes. As a general rule, it may be stated that the lower the melting-point of a fat employed as food, the more completely will it be absorbed; thus, olein is more readily utilised by the organism than palmitin or stearin, and food materials containing the former are not so likely to appear unchanged in the fæces as those containing the latter. In a case of cancer of the head of the pancreas, with complete biliary obstruction, we found that when the patient was upon a mixed diet the dried fæces contained 58.7 per cent. of "total fat," 41.4 per cent. of "neutral fat," and 17.5 per cent. of "fatty acid"; on a milk diet, however, the "total fat" was reduced to 26.2 per cent., the "neutral fat" to 25.9 per cent., and the "fatty acid" to 0.3 per cent.

The digestibility of fat, in the form of meat, is also influenced to a certain extent by the condition of the gastric secretion. We mentioned, when considering the physiology of pancreatic digestion, that collagen is not acted upon by pancreatic secretion; fat, therefore, which is enclosed in a mesh of connective tissue is liable to be protected from digestion in the intestine unless it has been previously acted upon in the stomach, so that deficiency or absence of hydrochloric acid in the stomach may lead to the appearance of an abnormal proportion of fat in the fæces.

An excessively fatty diet may also increase the fat content to an unusual degree, both normally and in cases of disease of the pancreas. In this connection we may mention that we have found that in some apparently

healthy persons there appears to be an inability to digest more than a very limited amount of fat, and, as their powers in this direction can, at least in some instances, be improved by the administration of preparations of pancreas, it is possible that the difficulty is due to a congenital or acquired deficiency of that organ.

In addition to diseases of the pancreas, biliary obstruction, defective gastric digestion, and excess of fat in the food, abnormal quantities of fat may be passed in the fæces from faulty absorption, due either to disease of the intestinal mucous membrane or to obstruction of the lymphatics. Such conditions are, however, comparatively rare, and are chiefly met with in extreme intestinal tuberculosis, amyloid disease, sprue, etc. Salomon states that purely functional disturbances of fat digestion may occur, but there is as yet little to substantiate this. The recognition and differentiation of the steatorrhœa met with in these conditions from that due to pancreatic disease can only be arrived at by attention to other signs, for the steatorrhœa itself presents no special characters by which it can be recognised. Thus in a case of intestinal tuberculosis we found that the "total fat" constituted 33.1 per cent. of the dry weight of the fæces, and that 21.4 per cent. of this was "neutral fat" and 11.7 per cent. "fatty acid." In another patient suffering from the same disease the fæces were found to contain 61.3 per cent. of "total fat," 42.5 per cent. of "neutral fat," and 18.8 per cent. of "fatty acid"—figures which closely resemble those met with in steatorrhœa of pancreatic origin. We have also had the opportunity of examining the fæces from a considerable number of cases diagnosed as sprue, and in all have found a large excess of fat, which consisted chiefly of "neutral fat." Although there is no doubt that, in this disease, the steatorrhœa is in part due to defective absorption, from atrophy of the mucous membrane of the intestine, we have come to the conclu-

sion that, in some instances at least, the condition is contributed to by concurrent disease of the pancreas. In one case of this description, in which we had reason to believe, from an examination of the urine and fæces, that the pancreas was diseased, material benefit followed an operation performed by one of us for the relief of pancreatitis. Before the operation the fæces showed 55.6 per cent. of "total fat," of which 51.4 per cent. was "neutral fat" and 4.2 per cent. "fatty acid." Six months after the operation, when the patient was put on a similar diet, there was 43.0 per cent. of "total fat," of which 22.3 per cent. was "neutral fat" and 20.7 per cent. "fatty acid"; thus suggesting that the fat-splitting process was being more efficiently carried out, and that a somewhat larger proportion of fat was being absorbed.

The *utilisation of proteids after complete and partial extirpation of the pancreas* has been investigated by Abelmann. He found that when the gland was completely removed in dogs, only 44 per cent. of the albumin given as food was absorbed, and that when a portion of the organ was left behind, 54 per cent. of the proteid was made use of. Some part of this deficient absorption he ascribed to the presence of undigested fat in the intestinal contents. Administration of pigs' pancreas to the depancreatised animals was found to increase the amount of utilised albumin to from 74 to 78 per cent. De Renzi and Cavazzani showed that after extirpation of the pancreas the amount of nitrogen in the fæces was increased, and Sandmeyer demonstrated that after partial extirpation of the gland from 62 to 70 per cent. of the albumin of the food was unused. Clinically, Hirschfeld found that in certain cases of diabetes, possibly due to disease of the pancreas, as much as 31.8 per cent. of the nitrogen of the food reappeared in the fæces, and Weintraud states that in a case of chronic pancreatitis, in which the diagnosis was confirmed post-mortem, 45.2 per cent. of the

ingested proteid was found in the stools. Müller reported that in his cases the absorption of proteids was only slightly affected.

The appearance of undigested muscle fibres in the stools has been described by numerous observers, both clinically and after partial or complete extirpation of the pancreas in animals. Fles, who was the first to draw attention to the value of this symptom in the diagnosis of pancreatic disease, states that in his case the muscle fibres disappeared after the administration of calf's pancreas. As stated in the table on page 214, our own investigations of the fæces have shown that undigested muscle fibres can be found more frequently in those cases where the functions of the pancreas are interfered with, than in those in which it is apparently normal, and that, since they were discovered in twenty out of twenty-four cases of cancer of the pancreas, but in only sixteen out of fifty-six cases of simple pancreatitis, their appearance in the stools, other things being equal, indicates a serious lesion of the gland. In some cases of pancreatic disease, undigested muscle can be detected in the stools with the naked eye, but, in the majority, they are only found on microscopical examination. It is impossible, however, to infer that the functions of the pancreas are disturbed from the appearance of muscle fibres in the fæces alone, for, excluding their presence from an excessive amount of meat having been taken in the diet, they may also be found in cases where, owing to increased peristalsis, or putrefactive changes, leading to secondary diarrhœa, they are hurried through the intestine before they have had time to be digested. Normally the stomach shares only to a slight extent, according to Schmidt, in the dissolution of muscle, its chief action being the digestion of the connective tissue of the meat; it is probable, however, that when the pancreatic juice is diminished or absent, gastric digestion may be continued lower down in the

intestine than is usually the case, and that consequently proteid digestion may not be as incomplete as might at first sight be expected. On the other hand, defective gastric secretion may lead to imperfect digestion of muscle, for the pancreatic juice being presented with more or less solid masses of fibres, bound together by connective tissue, can only attack them slowly from the surface, instead of dealing quickly with separated cells or groups of cells.

Reduction or failure of the pancreatic secretion might be expected to lead to *impaired digestion of starchy foods* and the appearance of an excess of carbohydrate in the stools. The observations made by various investigators on the fæces, however, have shown that only a small proportion, or none at all, of the carbohydrate taken in the food is excreted unchanged in cases where these conditions exist. According to Abelmann, 20 to 40 per cent. of the amylaceous material ingested reappears in the fæces in animals from which the pancreas has been extirpated, while Müller was unable to find any evidence that more carbohydrate was present in the stools of patients suffering from diseases of the pancreas than in those of normal individuals.

Our own investigations on the fæces in pancreatic disease tend to support the conclusions of Müller, on the whole; for, although we have found that in some instances a larger proportion of carbohydrate than is normally present in the stools of persons on a mixed diet could be detected, this was by no means constant, even in well-marked cases. The loss of weight and inability to accumulate fat, in spite of an abundant carbohydrate diet, points, however, to a diminished assimilation in excess of that indicated by the condition of the fæces, and it is probable that the figures given by analysis of the stools cannot be taken as a true index of the loss to the organism of carbohydrate material. The difference between the

amount assimilated and that present in the stools is probably to be explained by bacterial action, the starch of the food being slowly converted into maltose, and this in its turn being split up into lactic acid, acetic acid, alcohol, carbon dioxide, hydrogen, etc., by micro-organisms in the intestine. There is thus a loss of caloric potential which leads to inanition. The fact that many dyspeptics continue very thin, although they take an abundance of carbohydrate food, is possibly to be accounted for, as Herter suggests, by a diminution in the secretion of pancreatic juice, and the flatulence of which they complain may also be due to the consequent accumulation of carbon dioxide and other gases, while the drowsiness, with headache after meals, may arise partly from the absorption of alcohol and various organic acids.

It seems likely that in disease of the pancreas all the three chief ferments usually suffer diminution together, but there is reason to think that, under some circumstances, they are not diminished to an equal degree. In pancreatitis, due to obstruction or an ascending catarrh of the ducts, fat-splitting, proteolysis, and starch-conversion are no doubt equally affected, but it is said that in fever the ability to digest starches and fat may be much more impaired than the capacity of the pancreatic juice to act upon proteids, an observation which can only be explained on the assumption that trypsin under these circumstances is more abundantly secreted than the other ferments (Herter).

The stools in cases of advanced pancreatic disease generally present very typical characters; they are frequent, bulky, soft, white, have usually an acid reaction and a peculiar odour. Their bulk is partly to be attributed to the abnormal quantity of undigested material, particularly fat, passed through the bowel, and partly to the excessive fermentation which takes place in the lower part of the intestine. Their frequency is due in

part to their bulk, and is also no doubt contributed to by the excess of irritating by-products they contain.

Considerable difference of opinion exists as to the cause of the *white appearance of the fæces* when the pancreatic secretion is much diminished or excluded from the intestine. Müller, as we have seen, attributes steatorrhœa entirely to absence of bile, and, as it is well known that obstruction of the biliary passages gives rise to clay-coloured motions, he would refer the absence of colour also to that cause. Since many cases of pancreatic disease in which the typical white stools exist are associated with more or less complete blocking of the common bile-duct by gall-stones, or growth in the head of the pancreas, the absence of bile-pigment is without question a frequent contributory factor, but that it is not the complete and invariable explanation there is abundant evidence to show. We have on several occasions met with cases of pancreatitis with white stools where there was no jaundice, and no evidence of biliary obstruction at operation, and in which a chemical examination of the fæces demonstrated a well-marked reaction for stercobilin. The case already quoted on page 217, in which, after cholecystenterostomy, the whole of the bile, which had previously been escaping by a fistula, was turned into the small intestine, demonstrated very clearly that the presence of the biliary secretion is not sufficient to ensure a return of the normal colour when the pancreatic juice is still absent, for the appearance of the fæces was practically unchanged by the operation.

As far back as 1856 Claude Bernard, writing of dogs whose pancreas had been destroyed, stated that "it is remarkable that bile only colours the fæces a very bright yellow, whilst with the pancreatic juice the bile takes a very brown colour," thus suggesting that the pancreatic juice contributed indirectly to the colour of the fæces. Attention was drawn to this observation thirty-three years

later by T. J. Walker, in a paper read before the Royal Medical and Chirurgical Society, in which he described two cases of pancreatic disease where there were clay-coloured stools, although the liver and bile-passages were found to be normal post-mortem. He suggested that the white stools, to which he drew attention as indicative of disease of the pancreas, depended for their characteristic appearance upon the absence of the action of the pancreatic juice upon the bile-pigment they contained. This view has been supported by W. Gordon, who reported a case of pancreatic disease, with copious vomiting of green bile, in which the motions were sometimes clay-coloured and at other times cream or primrose-coloured, but never brown. Neither of these observers produced any evidence, beyond that afforded by mere inspection, that stercobilin was absent, or very much diminished, in the cases they report, nor did they take into account the enormous excess of fat present in the fæces in serious cases of pancreatic disease. It is to this large excess of fat that, in our opinion, the abnormal colour is chiefly due.

The evidence on which this opinion is based may be summarised as follows: (1) Quantitative examination of the stools from a large number of our cases has shown that the colour varies directly with the percentage of fat present, the largest amount being found in those specimens which are white to the naked eye, and the least in those which approximate to the normal colour. (2) The glistening white appearance is most marked in those specimens which are found microscopically to contain large numbers of fatty acid crystals, in part probably for the same reason that snow and other substances of a finely crystalline character appear white in mass. (3) The white stools on being heated on the water-bath assume a dark brown colour. (4) Removal of the fat with ether leaves a residue of a dark brown colour, similar to that obtained from normal fæces. (5) Stercobilin can be

demonstrated chemically in all specimens not derived from patients in whom there is complete obstruction of the bile-passage by cancer of the head of the pancreas, gall-stones, etc., the amount being proportional to the quantity of non-fatty residue. In cases of pancreatic disease associated with incomplete obstruction of the biliary passages the amount of stercobilin varies with the degree of obstruction. (6) The white stools occasionally met with in tuberculosis of the intestine, and some other conditions, where there is defective absorption of fat, are similar microscopically and chemically to those seen in typical cases of pancreatic disease, although there is no obstruction to the free flow of bile, and the pancreas is not affected.

These considerations point, we think, to an excess of fat in the stools being probably the most important element in the production of the white stools in serious pancreatic disease. But they do not exclude other and contributory factors, and that such exist is suggested by the fact that when such stools are exposed to the air they are sometimes seen to assume a darker colour on the surface. The acid reaction of the fæces in many cases is possibly associated with a modification of the flora of the intestine, and it appeared to us not improbable that this might cause a partial or complete reduction of the stercobilin to a colourless compound which, on contact with the oxygen of the air, was slowly converted into the normal colouring-matter of the stools. Experimental proof of this was sought by taking a specimen of normal, dark brown fæces, which had a faintly acid reaction, thoroughly mixing it with normal saline, so as to form a thin paste, and dividing it into two portions, which were placed in sterile test-tubes marked "A" and "B." The A-tube was plugged with wool and used as a control. To the B-tube was added, with a sterile platinum wire, a minute fragment of fæces from a typical

white pancreatic stool, and it was then plugged with wool. Both tubes were placed in the incubator and kept at 37° C. In twenty-four hours no change had taken place in the A-tube, but the lower part of the contents of the B-tube was distinctly lighter in colour than the upper portions, and than the control. The tubes were returned to the incubator and examined daily. The control and the upper part of the B-tube gradually became slightly darker, but the alteration in colour of the lower part of the latter previously noticed increased until the fourth day, when it was found to be of a light grey-brown appearance and presented a very marked contrast to the darker layers above. No further discharge of colour was observed, although the experiment was continued for several weeks.

This result, incomplete as it was, pointed to the presence in the pancreatic stool of organisms which, growing anaërobically, caused changes in the fæcal pigment that resulted in partial decolourisation. On repeating the experiment with specimens grown under anaërobic conditions a similar change was obtained, only that in this instance practically the whole of the inoculated tube was affected. On spreading this light-coloured material on a dish, and exposing it to the air, it slowly darkened and assumed very much its original appearance. On repeating the experiment with fæces of alkaline reaction no alteration in colour could be produced.

The very small proportion of fat in the particular specimen of fæces first submitted to experiment (5.3 per cent.) is against the changes observed being due to some alteration in that constituent, but it will be observed that we were unable to obtain with this specimen the dead-white appearance met with in characteristic cases of pancreatic disease, possibly because of the small proportion of fat it contained. It appears probable, therefore, that the characteristic white appearance of the stools met with in serious cases of pancreatic disease, in which there is no

obstruction of the biliary passages, is due chiefly to the presence of an excess of fat, particularly to the crystalline fatty acids, but partly also to the reducing action of bacteria growing anaërobically in an acid medium. In pancreatic disease associated with biliary obstruction the absence of bile-pigment, or its diminished amount, is also no doubt a contributory factor.

On referring to the table on page 214 it will be seen that in fifty-eight of the eighty cases in which there was evidence of disease of the pancreas the fresh fæces had an acid reaction, while in sixteen they were neutral or amphoteric to litmus, and in six distinctly alkaline. The presence or absence of jaundice appears to exert little or no effect upon the reaction of the stools when the pancreas is diseased, for the proportion in which they were acid is about the same in jaundiced and in non-jaundiced patients. In simple jaundice, unaccompanied by disease of the pancreas, and in cases where there were calculi in the biliary passages but no bile-pigment in the urine, on the other hand, the stools have generally been alkaline in reaction. This is probably to be attributed to the presence in pancreatic disease of free fatty acids, whereas in the non-pancreatic cases the excess of fat is due to combined fatty acids or soaps. The peculiar sour smell of the white stools in typical cases of diseases of the pancreas is also due, in all probability, to the higher free fatty acids they contain. Strasburger found, as a rule, a striking diminution in the amount of bacteria contained in icteric stools, in spite of the generally accepted view that bile possesses antiseptic properties. It is probable, therefore, that there is a lessened rather than an increased degree of putrefactive change in the fatty stools met with in such cases. Where, however, the amount of proteid residue is at the same time increased, as the result of pancreatic and intestinal affections, putrefaction may occur and the fæces become alkaline. Under these conditions

the acid reaction due to the fatty acids may be masked and the fæces be neutral, amphoteric, or even alkaline to litmus. The association of general enteritis, including chronic colitis, with disease of the pancreas may thus account for the alkaline reaction of the stools met with in a few cases.

The *blood changes* that result from diseases of the pancreas have not, as yet, received much attention from investigators, but that they are important and interesting is shown by the profound alterations in both its morphological and chemical characters that are met with in serious and advanced lesions, and to a less extent in milder types of disease. The hæmorrhagic tendency in pancreatitis, to which attention was drawn by one of us in the Hunterian Lectures for 1904, is an indication of the altered blood state induced by pancreatic lesions, and the changes in the urine to which we shall presently refer, also point in the same direction.

Besides hæmorrhagic pancreatitis, and the form of local hæmorrhage to which we have referred under the term "pancreatic apoplexy," there is in many pancreatic affections a tendency to general hæmorrhage, and patients often complain that they very readily bruise. The fact that this tendency is most marked in cancer of the head of the pancreas, and in pancreatitis associated with jaundice, naturally suggests that it is dependent upon the cholæmia, but since a hæmorrhagic tendency is also encountered in patients suffering from pancreatitis unattended by jaundice, it cannot be altogether due to that cause. Estimations of the coagulation time of the blood by one of us, with Wright's method, have shown that it may be prolonged in cases of cancer of the head of the pancreas to seven or eight minutes, or even longer, and that in pancreatitis with deep jaundice similar figures may be obtained. In pancreatitis without jaundice,

although the alteration is not so marked, coagulation times of four or five minutes are not uncommon.

We were at one time disposed to think that the explanation of the hæmorrhagic tendency, and the delayed coagulation time, in pancreatic disease might be dependent upon the presence of glycerine in the blood stream, derived from areas of fat necrosis, but we have not been able to obtain any experimental evidence in support of this theory, either directly by examining the blood or indirectly from the urine. It is well known that a diminution of the lime salts in the blood leads to a tendency to hæmorrhage, and that the hæmorrhagic tendency in pancreatic disease is dependent on this cause is highly probable for several reasons. We have found that the administration of calcium chloride to patients suffering from diseases of the pancreas not only reduced the coagulation time, often by several minutes, but is also an efficient preventive of the hæmorrhage that is liable to occur in such cases during and subsequent to operation. Further, the fact that pancreatic calculi contain 50 per cent. or more of calcium salts, whereas the normal secretion contains under 2 per cent., and the presence also of calcium oxalate crystals in the urinary deposit of many cases of pancreatitis, suggest that inflammation of the gland is associated with a disturbance of metabolism which results in an abnormal excretion of the lime salts and a consequent improverishment of the blood.

There is usually a diminution in the number of erythrocytes in pancreatitis which, in advanced and untreated cases, may be very marked indeed, even when jaundice is absent. Thus, in one case of chronic pancreatitis, in which operation was refused, we found 3,120,000 red cells per cubic millimetre; nine months later there were 1,889,000, and three months subsequently 1,501,000. In another case, where operation was followed by rapid improvement there were 3,472,000 red cells per cubic

millimetre before operation and 4,634,000 three weeks subsequently.

In some instances, and especially where the disease is of long standing, we have found that the hæmoglobin has not suffered a proportional decrease with the red corpuscles, and there has consequently been a high hæmoglobin index, similar to that found in pernicious anæmia. In one case of advanced chronic pancreatitis, which had previously been diagnosed as malaria, and in which a floating biliary calculus was removed from the common duct by one of us, a hæmoglobin index of 1.4, with 2,525,000 erythrocytes per cubic millimetre, was found shortly after the operation. Six months later the hæmoglobin index was 1.5, and a blood count showed 1,735,000 red cells per cubic millimetre. The patient passed from under our observation, but we have heard that he died shortly afterwards with all the symptoms of pernicious anæmia. Unfortunately no post-mortem examination was made. Another and similar case, where a hæmoglobin index of 1.5 and a red blood count of 1,293,000 were obtained, was examined after death, and the pancreas found to be small, hard, and cirrhosed. These cases suggest that in some instances inflammatory changes in the pancreas are liable to be associated with alterations in the blood, similar to those met with in so-called idiopathic pernicious anæmia, and that in making a prognosis in cases of pancreatitis the condition of the blood must be considered.

In our experience it is rare to meet with a well-marked leucocytosis in diseases of the pancreas, but up to the present our observations have been limited to cases of chronic pancreatitis and cancer of the gland. So far we have not had the opportunity of examining the condition of the blood in acute inflammation, but Woolsey in three cases of acute pancreatitis obtained leucocyte counts of 39,000, 17,600, and 26,000 per cubic millimetre respectively.

The changes met with in the urine in diseases of the pancreas arise in part from the altered conditions existing in the intestinal tract, and in part from perverted metabolism and excessive tissue waste.

Ethereal Sulphates and Indican.—Since a reduced secretion of pancreatic juice is followed by an impaired digestion of proteids, and these, as we have seen, are likely to be attacked and broken down by bacteria, it might be expected that the urine would in such cases show signs of excessive intestinal putrefaction, in the shape of an increased excretion of ethereal sulphates and a pathological excess of indican. According to Herter, this does in fact occur, for he states that when both the bile and pancreatic secretion are completely excluded from the intestine there is an excess of indican and the ethereal sulphates are always very largely increased, the proportion to preformed sulphates rising to 1 : 6, or 1 : 4, or even 1 : 1, as compared with the normal of about 1 : 10. Edsall, on the other hand, considers that a diminution in the amount of ethereal sulphates in the urine is an indication of pancreatic disease, for he points out that, although the products of proteolytic digestion are readily decomposed by bacteria, the native albumins are not. If, therefore, there is little or no proteolytic digestion going on in the intestine, as is the case in severe lesions of the pancreas, the products of bacterial activity will be lessened and the quantity of ethereal sulphates and indican in the urine decreased. Pisenti has estimated the amount of indican in the urine of dogs before and after tying the pancreatic duct. In one instance he found 11.70 to 19.90 mg. and in another 15.0 to 21.0 mg. per day, before the operation, as compared with 4.30 to 4.20 mg., and 6.0 to 9.0 mg., per day, respectively, after ligature, thus showing a marked diminution. The administration of pancreas-peptone to animals in which the duct had been tied he found increased the

quantity of indican excreted. In 1886 Gerhardi reported a case of pancreatic disease which he had successfully diagnosed during life from the absence of indicanuria, when the clinical symptoms suggested obstruction of the upper part of the intestine. Absence of indicanuria has also been observed by Stefanani in a case of purulent pancreatitis, and by Biondi in a case of adenoma of the pancreas. The question has been carefully investigated by Katz in depancreatised dogs. He states that when the animals were fed with easily digested and rapidly absorbed food, the excretion of ethereal sulphates was low—0.032, 0.022, 0.069 gram daily; but that when a diet of pure meat was substituted the daily excretion was unusually high—0.076, 0.089 gram, although readings as low as 0.024 were sometimes obtained even under these conditions. He also failed to detect any diminution in the amount of indican after lesions of the pancreas; in fact, in many instances there was marked indicanuria. On a pure meat and milk diet he found that there was an abundance of indican in the urine, the amount being greater, and its increase distinctly marked, on the day following the attack, especially in those cases where the animals took no nourishment after the operation, and even when they died quickly from duodenal necrosis. In those animals which long survived the operation no diminution in the excretion of indican was observed. Similar results have also been obtained by de Renzi. Schlagenhaufer records an increase of indican in a case of syphilitic interstitial pancreatitis that he investigated, and Hennige has referred the indicanuria found in cholera and lead-colic to an alteration in the pancreatic secretion caused by nervous influences.

Our own investigations of the relation between the preformed and ethereal sulphates in cases of pancreatic disease have given such varied results that we have come to the conclusion that they are due to factors which have

no direct relation to the activities of the gland. Similarly, although we have found an excess of indican in 49 per cent. of our cases of chronic pancreatitis and in 54 per cent. of cancer cases, there has been no relation between the intensity of the lesion and the degree of indicanuria. The truth appears to be that, although absence or a diminished secretion of pancreatic juice provides conditions under which there may be an abnormal production of aromatic derivatives in the intestine, these do not make their appearance in the urine unless there is at the same time some affection of the intestinal wall which facilitates absorption, and we have therefore come to look upon an excess of indican and ethereal sulphates in the urine in pancreatic diseases as an indication of an associated enteritis.

Bile.—Owing to the anatomical relations of the common bile-duct, the duct of Wirsung, and the head of the pancreas, circumstances which interfere with the free flow of the pancreatic secretion into the intestine are, in many cases, likely to obstruct the passage of bile at the same time, giving rise to jaundice and the appearance of bile in the urine. Hence the urine in diseases of the pancreas is frequently of a deep yellow or brown colour, and gives a reaction for bile-pigment. Bilious urine and jaundice are, however, by no means constantly found in diseases of the pancreas, even in pancreatitis associated with gall-stones in the lower part of the common bile-duct. Bile-pigment has been detected in the urine in 62 per cent. of our cases of chronic pancreatitis associated with cholelithiasis, and in only 16 per cent. of those in which no biliary calculi could be found in the common duct at the time of operation. Bile-pigment, in large amounts, was present in the urine of all the twenty-four cases of malignant disease of the pancreas included in the list on page 214.

The *relation of urobilin to the bile-pigments* has been the

subject of much controversy, but it is now generally accepted that if the bile is completely shut off from the intestine no urobilin can be found in the urine. The fact that the urine of only three of the above mentioned cases of malignant disease gave a reaction for urobilin is interesting in this connection, for they were the only three in which stercobilin could be found in the fæces. A pathological excess of urobilin was present in 61 per cent. of our cases of chronic pancreatitis with an obstruction of the common bile-duct, and in 40 per cent. of those in which no obstruction existed at the time of operation. The urobilinuria coexisted with jaundice, and the presence of bile-pigment in the urine, in 43 per cent. of the former, but in only 6 per cent. of the latter.

Azoturia.—Disturbances of intestinal digestion are said frequently to give rise to an increased excretion of nitrogenous compounds in the urine, but as the increase appears to be closely related to excessive putrefactive changes in the intestine, and, as we have seen, these are not by any means a constant accompaniment of diseases of the pancreas, no constant variation from the normal in this respect can be looked for. Azoturia is well known to occur in diabetes, and it has been observed, without glycosuria, by de Dominicus, Hédon, and Thiroloix after extirpation of the pancreas in animals. The excess is here, however, probably due to abnormal tissue destruction, for it is not met with after partial extirpation of the gland and is associated with a constant dextrose-nitrogen ratio. In most of our cases of pancreatitis the excretion of urea has not been excessive, the uric acid has varied little from the normal, and the total nitrogen, in the few cases in which we have estimated it, has fallen within normal limits. In cancer of the pancreas we have usually found that there was a subnormal proportion of urea.

The *excretion of phosphates* is said to be increased by disease of the pancreas, and de Dominicus states that

an increase of phosphoric acid is characteristic of pancreatic lesions, even in those cases where there is no glycosuria. But since the chief source of the phosphoric acid in the urine is the food, the nature of this will largely control the output. Thus David Young, experimenting with the case of pancreatic infantilism reported by Byrom Bramwell, found that when the patient was taking a milk diet the amount of phosphoric acid was extremely small, but that during the administration of pancreatic extract the quantity underwent a very marked and rapid increase. The explanation he offers is that the caseinogen of the milk was the source of the phosphorus in the urine. In the stomach it was broken up into paranuclein, containing 4 per cent. of phosphorus, and a proteid. Paranuclein itself is insoluble, but when it is acted upon by the alkaline pancreatic secretion it is dissolved and split into paranucleic acid and an albumose, from which the phosphoric acid of the urine was derived. We have been unable to detect any marked variation from the normal as regards the excretion of phosphates in any of our cases, and cannot confirm the statement of de Dominicus or the observation of Young, although with regard to the latter our investigations have been limited to two cases of malignant disease of the pancreas.

The *excretion of chlorides* in our cases of pancreatitis has not, as a rule, been noticeably disturbed, but we have found that in cancer of the pancreas the output has been frequently subnormal, possibly owing to the presence of pathological exudates.

Acetone Bodies.—Among the effects produced by extirpation of the pancreas in animals is the appearance of acetone, diacetic acid, and, occasionally, β-oxybutyric acid in the urine. Thus Baldi found 1.043 grams of acetone on the second day after the operation, 0.652 gram on the third day, and later 0.385 gram, 0.282 gram, and 0.049 gram, as compared with the normal of 0.0 gram to

0.105 gram. Minkowski observed that the excretion of these substances was most marked when the animals experimented upon became emaciated, and that the largest amounts of β-oxybutyric acid were found when the quantity of sugar was diminishing in the later stages of the disease.

Acetone and diacetic acid have been found in the urine in four out of the five cases of acute pancreatitis in which we have had the opportunity of investigating the urine, in 29 per cent. of our cases of chronic pancreatitis, and in 31 per cent. of the cases in which there was a malignant growth of the pancreas. The cases of chronic inflammation in which these substances were found were all of some standing and showed evidence of considerable tissue wasting. In one case where the pancreatitis had followed typhoid fever, and the patient was in an extremely serious condition when she came under our observation, the urine contained enormous quantities of both acetone and diacetic acid. Three days after operation the urine was again examined, and acetone bodies were found to be still present in very large amounts. As the patient was becoming comatose and her condition was serious, she was injected intravenously with three pints of normal saline solution. This caused a temporary increase in the excretion of the acetone bodies, but in about seventy-two hours they began to diminish, and six days after the injection they could no longer be detected. The patient's appetite and general condition improved at the same time, and she eventually made a complete recovery.

The source of the acetone bodies, both in wasting conditions and diabetes, has been much debated. It would appear that they are formed within the system and not in the intestinal tract, for the administration of purgatives does not diminish the quantity of acetone excreted in the urine; indeed, according to von Noorden,

it may occasionally cause an increase. The carbohydrates were at one time looked upon as the material from which they originated, but this view was discarded, and it was then supposed that they were formed in the process of disintegration of proteids. More recently attention has been turned to the fats, since β-oxybutyric acid and its derivatives, acetone and diacetic acid, can be derived from some fats by a simple chemical process, and at the present time this theory has the largest number of supporters. It is also possible, however, that they may arise synthetically within the body from simple carbon derivatives resulting from the breaking down of carbohydrates, proteids, and fats, and that this is a probable explanation is suggested by the conditions under which they may make their appearance in the urine and the circumstances that have been found to control the quantities excreted.

Calcium Oxalate.—In examining the urine from cases of pancreatic disease we were early struck by the frequent occurrence of well-marked deposits of calcium oxalate crystals in many of them. Further experience, now extending to some five hundred examinations, has only served to emphasise this early observation, and to suggest that there is probably a connection between chronic inflammatory lesions of the pancreas and oxaluria. Microscopical examination of the centrifugalised deposit from the urine has shown that oxalate crystals were present in 63 per cent. of our cases of chronic pancreatitis, or in 73 per cent. if those in which the urine contained bile-pigment be excluded. The crystals are generally numerous and are frequently very small, so that their nature can sometimes be only recognised by examining them with high powers of the microscope and by their chemical reactions. Quantitative examination in five cases has shown that the urine contained an actual excess of oxalic acid, and that the deposit was not merely caused

by physical conditions. Thus in one instance the output for twenty-four hours was found to be 0.03 gram, and in another 0.037 gram. We have not observed this condition in acute pancreatitis and rarely in cancer of the pancreas. Its association with chronic pancreatitis is interesting in view of the fact that a similar deposit of oxalate crystals is not infrequently met with in diabetes, and that a diminution in the output of sugar in this disease is accompanied by an increase in the oxalate deposit (vicarious oxaluria). Diabetes has also been noticed occasionally to follow long-continued oxaluria. Experimenting on dogs, J. Scott found that potassium oxalate was a depressing drug and that large doses increased nitrogenous metabolism, but he was unable to induce glycosuria by the subcutaneous injection of from 0.25 to 0.75 gram.

The origin of the oxalic acid in the urine is disputed. Part, no doubt, is directly derived from the food, but part probably arises from the breaking down of purin bodies within the organism. The experiments of Helen Baldwin show that, in dogs, the excretion of oxalates is increased by the administration of cane-sugar and glucose for long periods. Herter attributes this to the excessive fermentation and induced gastritis, but, since Ssobolew has shown that overfeeding animals with carbohydrates gives rise to changes in the islands of Langerhans, it is not improbable that the oxaluria found in these experiments, and in chronic pancreatitis, may be due to a disturbance of metabolism arising from changes in the functions of the cell islets.

Carbohydrates.—The alterations in the urine that we have so far considered, although sufficiently striking in many instances, are not peculiar to diseases of the pancreas. They probably result directly or indirectly from the disturbances of digestion, or from alterations of internal metabolism, to which the pancreatic lesions give rise, but they may also be brought about by other and quite distinct

causes. So far as experimental research goes, however, the appearance of certain carbohydrates in the urine is directly and peculiarly the result of a failure on the part of the pancreas to perform its functions in the internal economy of the body. The question of pancreatic diabetes will be fully considered in a subsequent chapter, so that it will be sufficient to mention here that extirpation of the pancreas in animals has been shown to give rise to the appearance of dextrose in the urine, and that more or less profound changes in the structure of the gland have been met with in many cases of human diabetes.

In addition to dextrose, however, other sugars have been described as present in the urine in a few cases of pancreatic disease. Le Nobel has described a case of glycosuria with fatty stools, in which there was a reducing substance in the urine having the characters of *maltose*. Von Ackeron found a similar substance in a case of pancreatic carcinoma. Rosenheim has recorded a case of maltosuria, with steatorrhœa and considerable loss of weight, in which interstitial pancreatitis was found post-mortem. A similar case has also been reported by Lepine. In an examination of two hundred and forty-five specimens of urine from cases of pancreatic disease by the phenylhydrazin test, we met with two in which an osazone having the characters of maltosazone was obtained in sufficient quantities for a careful examination, and five in which a small deposit of crystals, probably also maltosazone, was given. One of the former was a patient on whom an operation for stone in the common bile-duct had been performed five years previously. Maltosuria is thus a rare condition, and it is doubtful how far it is directly dependent upon disease of the pancreas.

Attention was first directed to the occurrence of *pentosuria* by the observations of Salkowski and Jastrowitz, who discovered a pentose in the urine of a morphine-eater, with temporary glycosuria, in 1892. Previous to this

observation pentoses had been met with only in plants, and it was believed that the animal organism was incapable of building them up. Subsequently two cases of pure pentosuria, without any dextrose, were described by Salkowski and Blumenthal. The excretion of pentose in these cases was found to be independent of the diet, and did not in any way affect the general condition of the patients. A diminution of the amount of indican was observed in both. On this account, but more particularly because the osazone obtained from the urine appeared to be identical in its appearance, melting-point, and solubilities with that obtainable from the pancreas, Salkowski assumed that the pentosuria was dependent upon an abnormally increased formation and destruction of the nucleo-proteid of that organ. This assumption derived support from the observations of Kulz and Vogel, who found that a pentose could be detected in the urine of starving dogs after removal of the pancreas. They also examined the urine of eighty diabetics and found a well-marked pentose reaction in sixty-four, in twelve the test gave doubtful results, and in four no reaction could be obtained. Salkowski and Blumenthal, however, were unable to detect any pentose in ten diabetics whose urine they carefully examined, and in none of the cases of inflammatory or malignant disease of the pancreas that we have investigated has any evidence of the presence of a pentose been found. Although Salkowski regarded pentosuria as an important indication of pancreatic disease, it is so rarely met with that it is of little practical value, and apart from the evidence already quoted, there is no proof that when present it is dependent upon lesions of the gland. It has also to be remembered that minimal traces of pentose may be met with after the ingestion of large quantities of plums, cherries, bilberries, and other substances comparatively rich in that variety of sugar. The pentose excreted under these conditions is, however,

the dextrorotatory form, whereas that met with in chronic pentosuria, of which a few cases have since been reported, is optically inactive.

The "Pancreatic" Reaction (Cammidge).—Although it cannot be considered as proved that the presence of a pentose in the urine is dependent upon disease of the pancreas, the results of the investigations that we have been carrying out since the early part of the year 1901 suggest that, in inflammatory lesions of the gland, there is excreted by the kidneys a substance which, on hydrolysis, yields a body giving the reactions of a pentose. The initial stages of these investigations were referred to and described in our Hunterian, and Arris and Gale lectures, delivered at the Royal College of Surgeons in 1904, and the results of further research were embodied in a paper read by one of us before the Royal Medical and Chirurgical Society in March, 1906.

The most striking indication of inflammatory lesions of the pancreas is undoubtedly furnished by the discovery of fat necrosis, either during life or post-mortem. This condition is most characteristically met with in acute and gangrenous pancreatitis, but it is not uncommon to find less marked changes in chronic inflammation of the gland, and it appeared to us possible that, even in those cases of chronic pancreatitis where no visual evidence existed of the fat-splitting process, there might still be molecular changes which could be recognized by the alterations produced in the chemical composition of the blood. The hæmorrhagic tendency we had noticed, and the microscopical changes found in the blood of patients suffering from diseases of the pancreas, pointed to there being some connection between the two conditions, and, bearing in mind the effects produced in animals by the subcutaneous injection of glycerine, it occurred to us that in man the continued action of minute doses, such

as fat necrosis would give rise to, might produce such a blood state as these patients exhibited.

Starting on the theory that there was some such connection between fat necrosis and the blood state found in pancreatic disease, we commenced our investigations by examining the blood of several cases of pancreatitis for glycerine and glycerine derivatives. But, as we quickly realised that such direct proof was not practicable, owing to the small amounts of blood available at the bedside, and to the relatively small quantity of glycerine likely to be present in it, we turned our attention to the urine, in the hope of finding indirect evidence in favour of our hypothesis. The well-known selective power of the kidneys, by which they detect and pick out abnormal constituents of the blood, favoured the view that the soluble products of fat necrosis, or their derivatives, might cause changes in the urine which, from the large bulk of material readily available for examination, could be satisfactorily detected. It is well known that glycerine on being boiled with nitric acid gives rise to glycerose, which can be recognised by the osazone that it forms with phenylhydrazin. When this test was applied to the urine from known cases of pancreatitis, the appearance of a much more marked deposit of crystals than was obtained from normal and most pathological specimens seemed at first sight to lend support to our theory, but as subsequent investigations showed that other mineral acids gave similar results, and it was found that the precipitate had not the characters of glycerosazone, it became necessary to look for some other explanation of the different behaviour of the urine from pancreatic and non-pancreatic cases.

Since comparative tests proved that cleaner and more satisfactory preparations could be obtained with hydrochloric than with nitric or sulphuric acid, it was adopted for routine work and the original nitric acid method aban-

doned. The procedure we made use of for our clinical investigations has been described under the term "the A-reaction," and was carried out as follows:

A specimen of the urine to be examined was carefully filtered, and 10 c.c. of the filtrate poured into a small flask. One cubic centimetre of strong hydrochloric acid (sp. gr. 1.16) was added, and, a small funnel having been placed in the neck of the flask to act as a condenser, it was placed on a sand-bath and gently boiled for from five to ten minutes, after the first sign of ebullition was detected (Fig. 97). A mixture of 5 c.c. of the filtered urine and 5 c.c. of distilled water was then poured into the flask, which was afterwards well cooled in running water. The excess of acid was now neutralised by slowly adding 4 grams of lead carbonate, and, after standing for a few minutes to allow of the completion of the reaction, the flask was cooled in water to the lowest possible temperature, and the precipitate removed by careful filtration through a well-moistened, close-grained filter-paper. The clear filtrate was then made up to 15 c.c., and added to 2 grams of powdered sodium acetate, 0.75 gram of phenylhydrazin hydrochlorate, and 1 c.c. of 50 per cent. acetic acid contained in a small flask fitted with a funnel-condenser. The mixture was gently boiled on a sand-bath for five minutes, poured into a test-tube, made up to 15 c.c., and allowed to cool undisturbed. After a period, varying with the severity

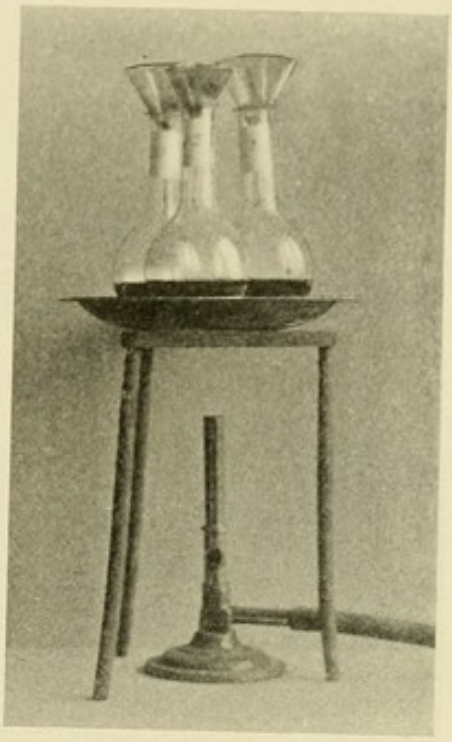

Fig. 97.—"Pancreatic" reaction flasks fitted with funnel condensers on a sand-bath.

of the case, of from one to twenty-four hours, a more or less abundant flocculent yellow precipitate, occupying a quarter or more of the test-tube, was seen to have formed, and this, when examined under the microscope with a $\frac{1}{6}$-inch objective, was found to consist of sheaves and rosettes of golden yellow crystals. The deposit met with in non-pancreatic urines was usually much less abundant, and had not, as a rule, the light flocculent appearance of that obtained in specimens from well-marked cases of pancreatitis.

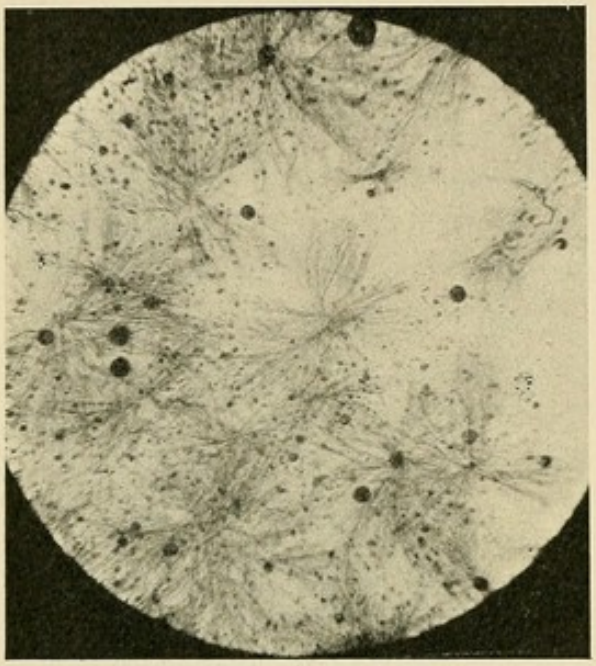

Fig. 98.—"Pancreatic" reaction-crystals, prepared by the A-method; from a case of acute pancreatitis (× 192).

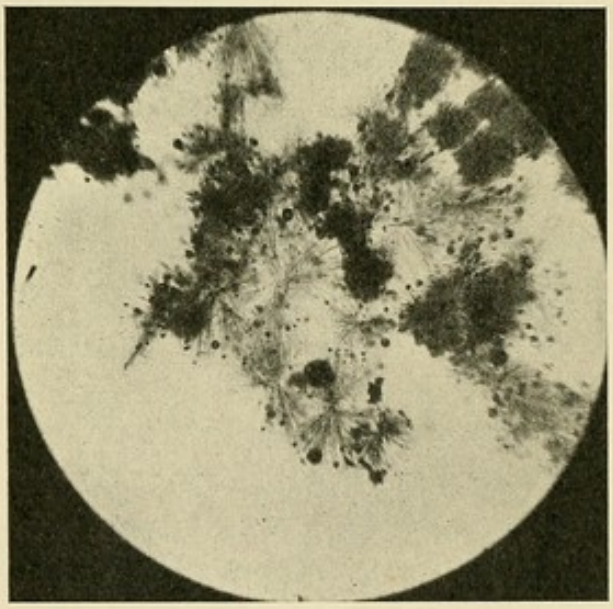

Fig. 99.—"Pancreatic" reaction-crystals, prepared by the A-method; from a case of chronic pancreatitis due to the presence of a gall-stone in the pancreatic portion of the common bile-duct (× 192).

Comparison of the crystals from different cases showed that they were not always of the same type, and experiments indicated that there was also a difference in their

solubilities. The crystals from cases of acute and sub-acute pancreatitis were found to be fine, slender, and hair-like in form, and on being irrigated with 33 per cent. sulphuric acid under the microscope were observed to disappear in under half a minute after the acid first touched them, taking the average of three or more determinations. In malignant disease, on the other hand, the more typical crystals were broad, coarse, and sword-like, and took from three to five minutes to dissolve in 33 per cent. sulphuric acid. Those from cases of chronic pancreatitis, and most non-pancreatic diseases, were intermediate in form and rate of solution, dissolving in dilute sulphuric acid in from one to two minutes after the acid first reached them. Exceptions were frequently met with, but careful observation of these

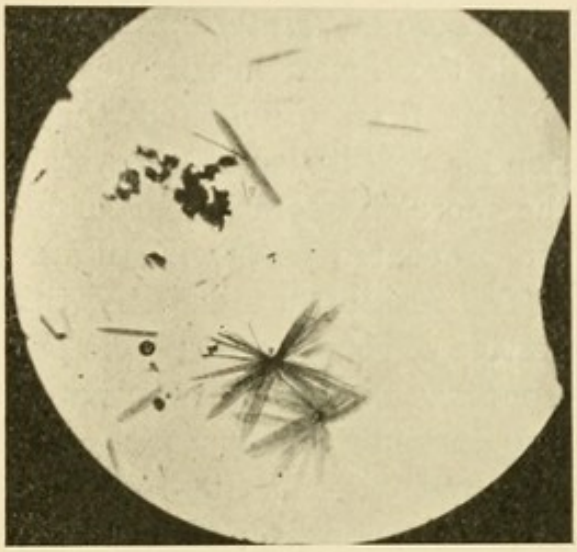

Fig. 100.—"Pancreatic" reaction-crystals, prepared by the A-reaction; from a case of malignant disease of the pancreas (× 192).

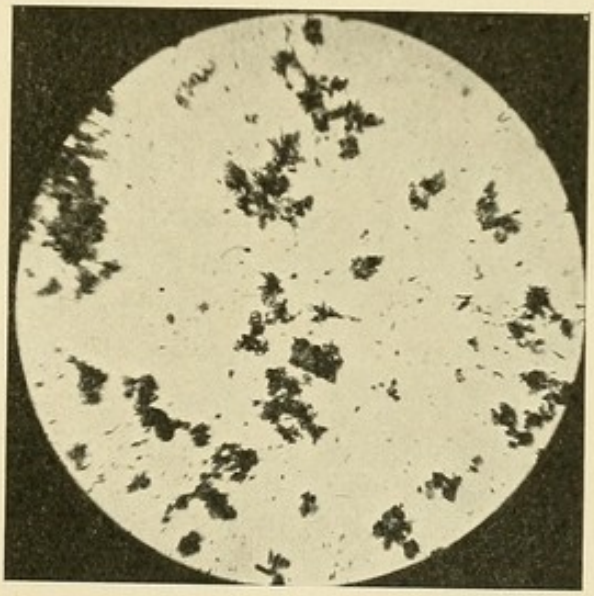

Fig. 101.—"Pancreatic" reaction-deposit from a normal urine treated by the A-method (× 192).

points was often found to be of considerable assistance in diagnosing the condition. The most striking exceptions were encountered in cases of pancreatic cancer, for while there was, in some cases, a much more abundant deposit than usual, and this was found to consist of slender readily soluble crystals, in others a deposit of the more characteristic, coarse crystals was only secured after repeated trials with different periods of boiling.

The results obtained by this method, although suggestive of some difference in the composition of the urine from pancreatic and non-pancreatic cases, and possibly also in different types of pancreatic disease, were not sufficiently distinctive to be entirely relied upon for purposes of diagnosis, and further investigation was obviously necessary. After considerable experiment we found that the formation of the crystals in the A-reaction was prevented, or interfered with, in inflammation of the pancreas by preliminary treatment of the urine with perchloride of mercury, while such treatment did not affect the appearance of the crystals in cancer of the pancreas and other conditions that gave rise to a positive reaction. This differential test, which we described as the "B-reaction," was carried out as follows:

Ten cubic centimetres of the filtered urine were thoroughly mixed with 10 c.c. of a saturated solution of perchloride of mercury in distilled water. After standing for a few minutes the mixture was filtered through a well moistened filter-paper, and to 10 c.c. of the filtrate 1 c.c. of strong hydrochloric acid was added. It was then boiled on the sand-bath for five to ten minutes, and diluted with 5 c.c. of the mixed urine and mercuric chloride solution with 10 c.c. of distilled water. After being cooled in running water the excess of acid was neutralised with lead carbonate and the succeeding stages of the operation carried out as in the "A-reaction."

The indications given by a comparison of the results

yielded by these two reactions proved, in our hands, of very considerable assistance in diagnosis, and enabled us to arrive at a correct opinion in several cases where the clinical signs and symptoms were doubtful or misleading. The results obtained in the examination of five hundred specimens of urine, two hundred and ninety-seven of which were from patients in whom there was evidence of pancreatic disease at operation or post-mortem, and two hundred and eighty-three from normal individuals or patients suffering from diseases in which there was no reason to think that the pancreas was involved, are shown in the subjoined table:

RESULTS OF THE "A AND B-PANCREATIC" REACTION IN FIVE HUNDRED CONSECUTIVE EXAMINATIONS.

Group.	Diagnosis.	No.	A Deposit Greater Than B.	A and B Deposit Equal in Amount.	A and B Both Negative.
I.....	Acute pancreatitis.....	4	4	..	..
II.....	Chronic pancreatitis:				
	(*a*) With obstruction of common duct....	68	49	19	..
	(*b*) No obstruction of common duct.....	116	98	15	3
III.....	Cancer of the pancreas .	29	8	21	..
IV.....	No pancreatitis:				
	(*a*) Gall-stones in gall-bladder or common duct	56	7	31	18
	(*b*) Miscellaneous.....	117	9	132	36
V.....	Normal.....	50	..	11	39

From this it will be seen that, as a rule, the deposit yielded by the A-reaction was greater than that obtained by the B-method in those cases where there was evidence of pancreatitis, but that in those instances where the pancreas was not inflamed there was no reaction, or the amount of precipitate was approximately the same in the

two preparations. In the majority of the cancer cases examined the result was similar to that obtained in non-pancreatic disease, but in about 25 per cent. there was an appreciable difference in the amount of deposit yielded by the A- and B-reactions.

Like most comparative tests, to which accurate measurements cannot be applied, this method suffered from the great disadvantage of being dependent, to a certain extent, on the experience of the observer for its interpretation. Further, unless considerable care was exercised in the details of the experiment errors in technique were liable to occur and confuse the issue, as the published accounts of some who have attempted to use these reactions for diagnostic purposes have shown. To overcome these difficulties and, as far as possible, eliminate the personal element, we have introduced an "improved" or "C-reaction," in which the presence or absence of pancreatitis is indicated by the examination of a single preparation. The manipulation is slightly more complicated and still requires a reasonable amount of skill and care, particularly in the details of the experiment, but the result is an absolute one, and is therefore independent of the personal bias of the investigator.

Examination of the phenylhydrazin precipitate derived from the urine in cases of pancreatic inflammation, after treatment with hydrochloric acid, showed that it consisted of two parts, one a phenylhydrazin compound of glycuronic acid and the other the osazone of a sugar. Although there is reason to believe that the excretion of glycuronic acid is increased in pancreatitis, an augmentation of the output occurs in so many pathological conditions that no helpful diagnostic method could be based upon this, in the present state of our knowledge. On turning to the precipitate obtained from the urine after treatment with mercuric chloride we found that it consisted entirely, or almost

entirely, of a glycuronic acid compound of phenylhydrazin, so that the difference noticed between the A- and B-reactions in characteristic cases of pancreatic inflammation appeared to be dependent upon the presence of the sugar. By collecting large quantities of urine from well-marked cases of pancreatitis, we are able to investigate the characters of this, and found that it gave the reactions of a pentose. As we have already said, we have been unable to discover any evidence of the presence of a pentose in the untreated urine from any of our cases, so that it was probable that the pentose giving rise to the characteristic "pancreatic" reaction was formed by hydrolysis from some antecedent substance in the urine during the process of heating it with the dilute acid.

We are not as yet in a position to make any definite statements with regard to the nature of the mother-substance from which the sugar is derived, but our earlier experiments proved that it was not the so-called animal gum of the urine, and the fact that a positive reaction has not, so far, been obtained by the "improved method" with the urine from any but pancreatic cases suggests that it is probably a body resulting from changes in the pancreas, and possibly derived directly from that organ. The relatively large proportion of pentose-yielding material in the pancreas, as shown by Neuberg, who gives the following as the results of his analyses of various organs:

Pancreas	2.48%	As pentose in the dry substance
Liver	0.56%	
Thymus	0.56%	
Submaxillary gland	0.53%	
Thyroid	0.50%	
Kidney	0.49%	
Spleen	0.46%	
Brain	0.22%	
Muscle	0.11%	

points to the pancreas as the most likely source. It cannot be denied, however, that the disintegration of other tissues may also, at times, influence the urine in this

respect, and it has also to be remembered that the ingestion of large amounts of penton-containing food materials may also cause small quantities of pentose to be excreted in the urine; therefore, while we maintain that a positive reaction by the "improved method" of performing the so-called "pancreatic reaction" is strongly suggestive of inflammatory disease of the pancreas, we are not prepared to contend that it is pathognomonic of pancreatitis.

The "improved method," or "C-reaction," is based upon the different behaviour of glycuronic acid and the sugars, in acid solutions, to tribasic lead acetate, the former being precipitated and the latter remaining in solution. If therefore the acid filtrate, left after the urine has been boiled with hydrochloric acid and the excess of acid neutralised with lead carbonate, is treated with tribasic lead acetate, the glycuronic acid set free in the process will be thrown out, while any sugar remaining in the solution can be detected by the phenylhydrazin test, after the precipitate has been filtered off and the excess of lead removed by appropriate methods.

In performing the reaction a specimen of the twenty-four hours urine, or of the mixed evening and morning secretions, is filtered several times through the same filter-paper. If it is found to be free from sugar and albumin, and is acid in reaction, 2 c.c. of strong hydrochloric acid (sp. gr. 1.16) are mixed with 40 c.c. of the clear filtrate, and the mixture gently boiled on a sand-bath in a small flask, fitted with a funnel condenser (Fig. 97). After ten minutes' boiling the flask is well cooled in a stream of water, and the contents made up to 40 c.c. with cold distilled water. The excess of acid is then neutralised by slowly adding 8 grams of lead carbonate. After standing for a few minutes to allow of the completion of the reaction, the flask is again cooled in running water, and the contents filtered through a well-moistened, close-grained filter-paper until a perfectly clear filtrate is obtained. The acid filtrate is

then well shaken with 8 grams of powdered tribasic lead acetate, and the resulting precipitate removed by filtration, as clear a filtrate as possible being secured by repeating the filtrate several times if necessary. Since the large amount of lead now in solution would interfere with the subsequent steps of the experiment, it is removed, either by a stream of sulphuretted hydrogen, or, what we have found to be equally satisfactory and less disagreeable, by precipitating the lead as a sulphate. For this purpose the filtrate is well shaken with 4 grams of powdered sodium sulphate, the mixture heated to the boiling-point, then cooled to as low a temperature as possible in a stream of cold water, and the white precipitate removed by careful filtration. Ten cubic centimetres of the perfectly clear, transparent filtrate are taken and made up to 17 c.c. with distilled water; it is then added to 0.8 gram of phenylhydrazin hydrochlorate, 2 grams of sodium acetate, and 1 c.c. of 50 per cent. acetic acid, contained in a small flask fitted with a funnel condenser. The mixture is boiled on a sand-bath for ten minutes and filtered hot through a small filter-paper, moistened with hot water, into a test-tube provided with a 15 c.c. -mark. Should the filtrate fall short of 15 c.c., it is made up to that amount with hot distilled water, the added water being well mixed with the fluid by stirring with a glass rod, but in our own work we find that any addition is rarely necessary, as, with a little practice, it is possible to so regulate the boiling that the final result almost always comes out at between 15 and 16 c.c.

In well-marked cases of pancreatic inflammation a light yellow, flocculent precipitate should appear in a few hours, but in less characteristic cases it may be necessary to leave the preparation over-night before a deposit occurs. Under the microscope the precipitate is seen to consist of long, light-yellow, flexible, hair-like crystals arranged in delicate sheaves, which

when irrigated with 33 per cent. sulphuric acid melt away and disappear in ten to fifteen seconds after the acid first touches them. The preparation must always be examined microscopically, as a small deposit may be easily overlooked with the naked eye, and it is also difficult to determine the exact nature of a slight precipitate by macroscopical investigation alone.

To exclude traces of sugar, undetected by the prelimi-

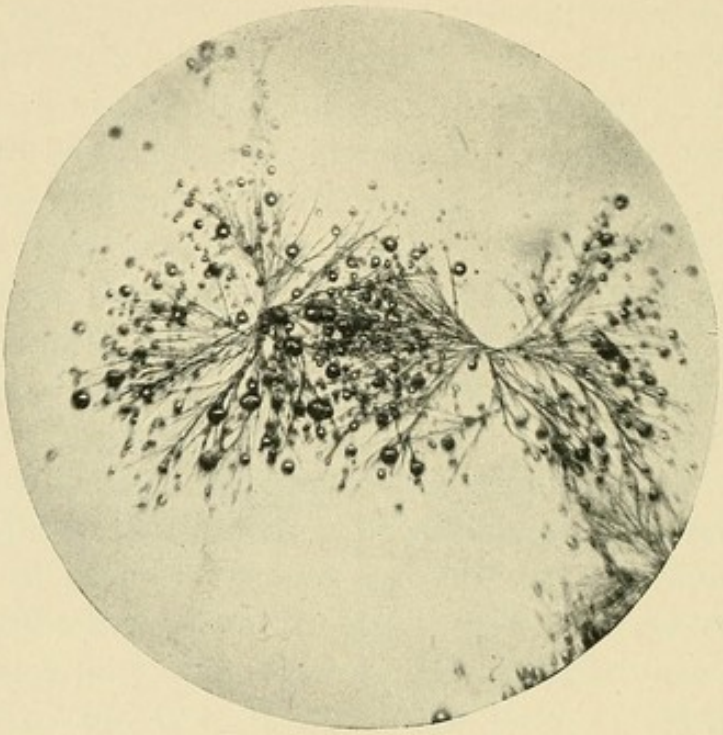

Fig. 102.—Improved, or C-, "pancreatic" reaction-crystals from a case of chronic pancreatitis with gall-stones in the common bile-duct (× 200).

nary reduction tests, a control experiment is carried out by treating 40 c.c. of the filtered urine in the same way as that in the test just described, except that it is not boiled with hydrochloric acid. Any albumin that may be present in the urine is removed, previous to commencing the test, by faintly acidulating, boiling, filtering off the albuminous precipitate, cooling, and making the specimen up to its original bulk with distilled water. The urine employed for

the experiment should be fresh, and not have undergone fermentative changes. If alkaline in reaction, it should be made distinctly acid with hydrochloric acid before the test is commenced. Any dextrose that may be present can be removed by fermentation *after* the urine has been boiled with the acid and the excess neutralised. The administration of calcium chloride, as advised by one of us in all cases of pancreatic disease previous to operation, has been found to interfere with the success of the reaction.

In the following table the results obtained by this method in two hundred consecutive examinations, in which it has been possible to confirm the diagnosis post-mortem or at operation, are given, and, for the sake of comparison, the findings in fifty specimens from presumably healthy persons are also included:

RESULT OF THE "IMPROVED" OR "C-PANCREATIC REACTION" IN TWO HUNDRED AND FIFTY CONSECUTIVE EXAMINATIONS.

Group.	Diagnosis.	No.	Positive.	Negative.
I	Acute pancreatitis	2	2	..
II	Chronic pancreatitis:			
	(*a*) With obstruction of the common duct:			
	(1) By gall-stones	19	19	..
	(2) By growth	2	2	..
	(*b*) No obstruction of common duct:			
	(1) No gall-stones found	32	32	..
	(2) Gall-stones in gall-bladder	12	12	..
III	Cancer of the pancreas	16	4	12
IV	No pancreatitis:			
	(*a*) Gall-stones in common duct	10	..	10
	(*b*) Gall-stones in gall-bladder	11	..	11
	(*c*) Miscellaneous	96	4	92
V	Normal	50	..	50

It will be seen that a positive reaction was obtained in seventy-five, and that in one hundred and twenty-five no crystalline deposit was observed. Two of the former were cases of acute pancreatitis. In thirty-three there was chronic pancreatitis, associated with gall-stones in the common duct in nineteen, with growth of the common duct invading the pancreas in two, and with stones in the gall-bladder in twelve. In twelve, although the pancreas was stated to be distinctly larger and harder than normal when examined at operation, no biliary calculi were found, but in one of these cases gall-stones were found in a specimen of fæces examined at the same time as the urine, and in another several had been found in the stools shortly before the examination was made. There was an ulcer of the duodenum in six, a gastric ulcer adherent to the pancreas in one, in three there were numerous adhesions about the head of the gland. Of the sixteen cases of cancer of the pancreas, twelve gave no reaction, but in four a more or less marked deposit of crystals was obtained. In addition to the twelve cases of cancer just mentioned, no reaction was obtained in ten specimens from cases where gall-stones were found in the common duct at the time of operation and the pancreas was said to be normal; in eleven where biliary calculi were present in the gall-bladder, but no evidence of pancreatitis was found either pathologically or clinically; and in ninety-two samples from cases of miscellaneous diseases, including cancer of the stomach, colon, rectum, or liver, gastric ulcer, duodenal ulcer, gastritis, colitis, appendicitis, tuberculosis of the intestine, intestinal obstruction, cirrhosis of the liver, hepatic abscess, nephritis, floating kidney, tuberculosis of the kidney, cystitis, mumps, and Addison's disease. In four cases of cancer of the stomach or duodenum a positive reaction was obtained, but in these the growth was adherent to the pancreas. One, in which the growth was situated in the

first part of the duodenum, gave no reaction when first examined, and on abdominal section it was then found that the pancreas was free; but a month later, when a positive reaction was obtained, a second exploratory operation showed that the pancreas had become involved in the growth. No reaction was obtained with any of the fifty specimens from apparently healthy individuals. On looking through the table it is interesting to note that nineteen out of the twenty-nine cases (or 65 per cent.) in which gall-stones were found in the common duct at the time of operation gave a positive reaction, whereas ten (or 35 per cent.) gave no reaction, which corresponds fairly closely with the 62 per cent. and 38 per cent. given by Helly as the proportion of cases in which the common bile-duct is embraced by, and free from, the pancreas respectively.

The urines from twenty-two cases, which previous to operation had given a well-marked reaction, were re-examined one to two weeks after cholecystenterostomy had been performed for the relief of pancreatitis, but no reaction could be obtained, and in four cases where an opportunity presented itself of making a further investigation at a subsequent date, one three months, another six months, a third seven months, and the fourth nine months after operation, there was still no reaction.

It has been possible to test the findings of the "pancreatic" reaction in twenty-four cases by histological examination of the pancreas. In one a small piece of the gland was removed at operation and showed evidence of interstitial pancreatitis, which confirmed the diagnosis based upon the urine examined. The remaining twenty-three were examined post-mortem. Three were cases of cancer of the pancreas. In one, where the whole organ was invaded by the growth, the results of the examination of the urine had suggested during life that there was a considerable chronic inflammation; in the other two

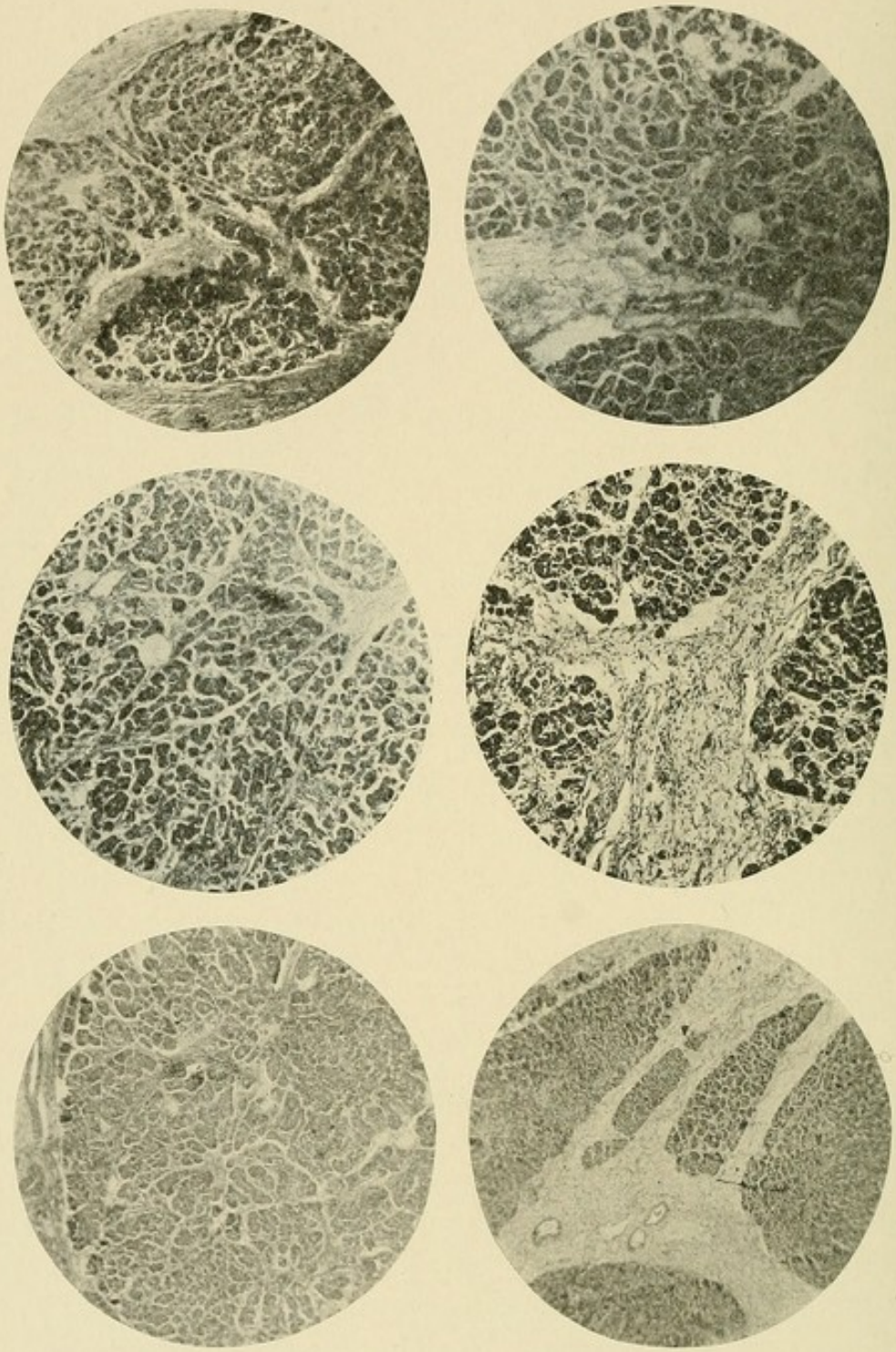

Fig. 103.—Microphotographs of the pancreas from six cases the urine of which had given during life a well-marked "pancreatic" reaction (× ca 40).

the disease chiefly affected the head of the gland and a correct diagnosis had been arrived at. Eleven had been diagnosed from the urinary reaction as chronic pancreatitis. In ten of these a more or less marked overgrowth of the interstitial connective tissue was found microscopically (Fig. 103). It is noteworthy that in four of them, although the organ had been said at operation to be larger and harder than usual, no pathological change could be detected by the naked eye after death. In one case no interstitial overgrowth could be discovered either macroscopically or microscopically, but the blood-vessels were much dilated and there were small patches of round-celled infiltration in the neighbourhood of the ducts, pointing to an early inflammatory change. No reaction suggestive of a pancreatic lesion had been obtained in the remaining nine cases during life, and post-mortem the pancreas appeared to be normal, both to the naked eye and on microscopical examination.

It has been contended by Ham and Cleland that the crystals obtained from the urine by the A- and B-reactions are crystals of a lead salt, formed by the action of phenylhydrazin and sodium acetate upon the lead carbonate used in neutralising the hydrochloric acid employed in the test, and that therefore the results obtained by these methods are absolutely unreliable. The unsoundness of this argument is at once apparent when it is remembered that sulphuric acid, neutralised with barium carbonate, or nitric acid neutralised with urea, give similar results, and that hydrochloric acid was only selected for routine work because it gave cleaner preparations and its action was more easily controlled. Lead carbonate was selected as the neutralising agent, since the caustic alkalies were found to interfere with the reaction, and lead was the most insoluble chloride that could be formed.

There are possibly some, however, who, in consequence

of this and similar criticism, are unconsciously biased against the reaction, and on this account it may not be out of place if we here summarise the arguments brought forward by these and other writers, and briefly consider the experimental data on which they were based.

The conclusion reached by Ham and Cleland was arrived at on the following grounds: (1) They stated that they were able to obtain crystals from all urines, provided that the solution was sufficiently concentrated by boiling; (2) rosettes of pale crystals were also obtained when the reaction was performed with distilled water; (3) if the urine or distilled water, after being boiled with hydrochloric acid, and neutralised with lead carbonate, was treated with ammonium sulphide, filtered, and boiled, the reaction with phenylhydrazin was prevented; (4) lead acetate solution treated with sodium acetate and phenylhydrazin hydrochlorate gave fine needle-like crystals in rosettes and sheaves.

There is no doubt that a soluble lead salt does form needle-like crystals when boiled with sodium acetate and phenylhydrazin hydrochlorate, but these crystals never appear in a properly performed "pancreatic" reaction, and, should they do so, can be easily distinguished from the true osazone crystals by the naked-eye characters and their appearance under the microscope. They are very much larger (Fig. 104), colourless instead of yellow, and form solid masses at the bottom of the test-tube or appear as tufts adherent to its walls. In a carefully performed reaction the quantity of lead that passes into the filtrate is small, and does not in any way affect the results of the test, but if, from faults of manipulation or errors in technique, a large amount is present, it is not unlikely to give rise to difficulties in inexperienced hands, especially when the preparation has been unduly concentrated by excessive or furious boiling. It is to this cause that the positive reactions

obtained by Ham and Cleland with all urines and with distilled water were no doubt due. The removal of any lead in solution, moreover, does not interfere with the success of the reaction, as these writers state; indeed, this is intentionally done in the "improved reaction," as there the large amount of lead acetate employed would

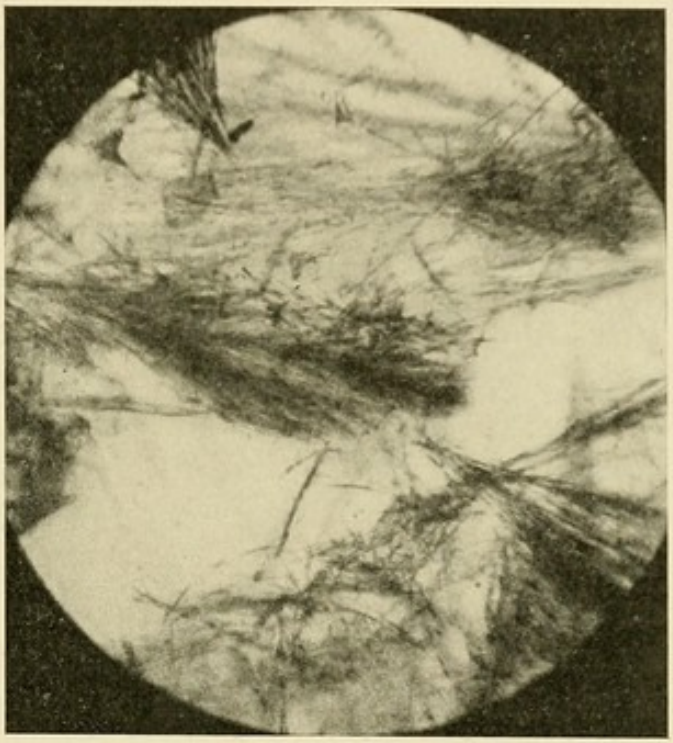

Fig. 104.—Microphotograph of the "lead-salt crystals" formed as the result of faulty technique in carrying out the "pancreatic" reaction by the original A-method (× 200).

introduce a serious difficulty, unless it were removed before performing the phenylhydrazin test. Ammonium sulphide cannot, however, be used for the purpose, as the ammonia set free destroys any sugar that may be present when the fluid is subsequently heated, but Ham and Cleland do not appear to have considered that, when using ammonium sulphide in the manner they describe, they were possibly performing a modification of Moore's test for sugar. Finally, the fact that the purified crystals

from the urine in cases of pancreatic disease have a definite melting-point, are free from any trace of lead, and correspond in their other characters with osazone crystals, conclusively proves that, when the reaction is carefully and properly performed, they are not "lead salt crystals."

In a paper on "the use of phenylhydrazin in the clinical examination of urine" W. H. Willcox gives an account of some experiments which were, more or less, based upon the reactions described in our original communications, and he there states that "the production of characteristic yellow crystals in the urine after hydrolysis with hydrochloric acid can in no sense be used as a specific test for any pathological conditions, since such crystals are constantly obtained from normal urines." The experimental portions of this paper cover much of the ground traversed by us previous to the elaboration of the "pancreatic" reaction, but we cannot confirm all the results or agree with the deductions drawn from them. We are quite willing to admit that "the production of characteristic crystals in the urine after hydrolysis cannot be used as a specific test for any pathological condition," including pancreatitis, if the method employed is that of the author of that paper, but we do maintain that, if the methods we have described are carefully and conscientiously carried out, and the results considered in conjunction with the clinical symptoms, and the indications given by other methods of pathological research, the presence of pancreatitis can be determined with very much greater certainty than by the clinical evidence alone. Our results with normal urines do not correspond with those obtained by Willcox, as the tables on pages 249 and 255 show. We do not think that any difficulty of diagnosis was likely to arise even with a normal urine when the original A- and B-reactions were employed, but the "improved method" has now got rid of any slight difficulty that there

might possibly be and has simplified the diagnosis of pancreatitis from non-pancreatic diseases.

J. H. Schroeder and P. S. Haldane have published some criticisms of our original methods under the mistaken idea that we claimed to have proved the presence of glycerine in the urine of patients suffering from diseases of the pancreas. The glycerine theory was but a working hypothesis on which we commenced our investigations, and, as we have explained, had to be abandoned as the research proceeded. They also assume that the crystals obtained in acute and chronic pancreatitis and in cancer of the pancreas by the A-reaction are identical, and point out that they are therefore unlikely to have different shapes and solubilities. The assumption is without foundation, for the difference in appearance and in rate of solution in sulphuric acid is due to the differences of chemical composition.

Fat-splitting Ferment (Opie).—Since the fat necrosis associated with acute pancreatitis is due to the fat-splitting ferment of the pancreatic juice, it occurred to Opie that this ferment, which is free in the tissues, might be excreted by the kidneys. In one case, in which he tested the truth of this assumption, he found evidence that tended to show that such an excretion did occur. The specimen of urine examined was taken, after death, from the body of a man who died of hæmorrhagic pancreatitis. It was neutralised with potassium hydrate and divided into two parts. To one a few drops of ethyl butyrate and a little neutral litmus were added. The other was treated in the same way, after any ferment present had been destroyed by boiling. Both specimens were incubated at 37° C. for twenty-four hours. At the end of that time the unboiled specimen had acquired a well-marked acid reaction, while the control specimen showed little, if any, change. We have not had the opportunity of carrying out a similar test in a case

of acute inflammation of the pancreas, but in two cases of subacute pancreatitis, and several of chronic pancreatitis, in which we have employed it no difference could be observed between the two preparations.

Lipuria has been described by some writers as occurring in disease of the pancreas. Clark and Bowditch have reported cases of cancer of the gland in which fat globules were present in the urine. Tulpius and Elliotson also record similar cases, but without any other confirmatory evidence of pancreatic disease than the presence of fat in the stools. In a case of acute pancreatitis, operated on seventy-two hours after the onset, Cooke found fat in the urine on one occasion. We have met with lipuria only once in our series of cases, and that was in a case of chronic pancreatitis in a woman, aged forty-four, the cause being apparently an extension from duodenal catarrh. It was associated with liporrhœa, azotorrhœa, and bulky stools, and with a well-marked pancreatic reaction in the urine. The abdomen was opened and a swelling of the pancreas was discovered with a number of adhesions surrounding it, but no gall-stones were found. Drainage of the bile-ducts by a simple cholecystotomy completely cured the pancreatic condition, and when the urine was examined a year later there was an entire absence of the pancreatic reaction.

Fat is met with in the urine in so many different conditions, and is so rarely found in pancreatic disease, that its association with lesions of the pancreas is possibly accidental. It is to be remembered, however, that lipuria occurs in diabetes mellitus, and that in this disease a large amount of fat is also occasionally encountered in the blood.

Detection of Pancreatic Enzymes.—It is sometimes necessary to determine whether a pathological fluid, obtained from a cyst or fistula, has originated in connection with the pancreas. The general physical and chemical characters of the fluid may afford some indication of its probable source,

but the most reliable proof is obtained by an investigation of its behaviour to proteids, fats, and carbohydrates. When the fluid is found to contain ferments capable of readily digesting all three forms of food material there can be little doubt as to its origin. The presence of a diastatic ferment alone is of little value in diagnosis, since diastase may be met with in other fluids of the body. The detection of a proteolytic ferment, capable of digesting albumin in an alkaline medium, is much more important, for no other ferment than trypsin can dissolve albumin in the presence of an alkali. It is frequently found, however, that the contents of cysts, undoubtedly of pancreatic origin, have little or no proteolytic power. This is stated to be particularly the case with old encapsuled cysts of long standing. It has to be remembered, however, that the normal pancreatic juice possesses but feeble powers of digesting proteid until it has been activated by the enterokinase of the intestine, so that the absence of this property in the contents of pancreatic cysts is not surprising. The observation of Delezenne that the addition of a small quantity of a soluble calcium salt activates the pancreatic secretion as powerfully, but more slowly, than enterokinase suggests a way of overcoming the difficulty when examining the contents of a cyst for diagnostic purposes. The power of splitting neutral fats into glycerine and fatty acids is the most characteristic property of pancreatic juice, and unless a pathological fluid possesses this property it cannot be stated, with certainty, that it has originated in connection with the pancreas.

The method of testing for the *proteolytic ferment* developed by Boas is that which has been usually employed. The fluid to be examined is added to milk, placed for some time in an incubator, and, after the casein has been precipitated, is examined by the biuret reaction. A positive result of the test indicates that the fluid can digest albumin in the presence of an alkaline reaction.

Pawlow, in his investigations of the digestive juices, employed Mett's tubes, and these have the advantage that they afford a means by which the digestive power of the fluid can be expressed numerically for purposes of comparison. Egg-albumen is employed in this method and the tubes containing it are prepared as follows: The egg-albumen is filtered through gauze into a small beaker, or wide test-tube, and short glass tubes, having a lumen of about 2 mm., are slowly dropped into it. Air-bubbles are allowed to escape, aided by gentle tapping, and the vessel containing the tubes is then placed in a bath of boiling water for five or ten minutes. The flame is removed and the glass allowed to cool for several hours. The test-tube or beaker is then broken, and the small tubes filled with, and embedded in, the coagulated albumen are cut out and preserved in glycerine. One of the tubes is used for each test. It is first washed with water, then placed in a test-tube containing the fluid to be tested, which, if necessary, has previously been made faintly alkaline. After being incubated for from three to ten hours, the small tube is examined and the presence of a proteolytic ferment is shown by a portion of the column of coagulated albumen having been dissolved. To determine the digestive power of the fluid, the length of the tube, and of the undigested remains of the proteid column, are measured off on a millimetre scale with a low power of the microscope; the difference gives the length of the digested cylinder in millimetres and fractions of a millimetre. The quantity of proteolytic ferment in the fluid is proportional to the square of the column of albumen digested in a definite time.

The *fat-splitting ferment* may be tested for by the method of Castle and Loevenhart, in which purified ethyl butyrate and neutral litmus are added to the fluid to be examined (see "Opie's test" for fat-splitting ferments in the urine, page 263). A neutral fat, obtained by tho-

roughly shaking olive oil with sodium carbonate solution and ether, pipetting off the ethereal layer, filtering it if necessary, and then recovering the fat from the ether by allowing the latter to evaporate, may be used instead of ethyl butyrate. A numerical expression of the fat-splitting power of the fluid may be obtained by titrating the acidity of the emulsion, after it has been incubated for a definite period with periodical shaking, with baryta solution.

The *diastatic ferment* can be recognized by incubating the fluid with boiled starch paste, and then testing for sugar with Fehling's solution. The activity of the ferment may be determined by titrating the sugar, formed in a given time from a definite amount of starch paste, with Fehling's solution, but the more rapid method advocated by Pawlow gives results that are sufficiently reliable. This is a modification of Mett's method for proteolytic ferments. Thin glass tubes filled with coloured starch paste are incubated with the fluid to be tested for a definite time,—half an hour is usually sufficient,—and then examined with a lower power of the microscope. The activity of the amylolytic ferment is found to follow the same law as the proteolytic and vary directly as the square of the column digested in a given time.

In all investigations on the digestive power of fluids it is advisable to conduct a control experiment with a portion of the material that has been boiled to destroy any ferments that may be present, so that in making the final deductions it may be used as a standard of comparison. The action of bacteria should also be excluded by adding to both the test fluid and to the control a mild antiseptic, such as thymol.

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CHAPTER XI

DIABETES

The dependence of diabetes upon disease of the pancreas was first suggested by Bouchardat in 1875, and, although two years later Lancereaux emphasised the importance of the connection, and sought to distinguish a special type of the disease which he believed was always associated with profound alterations in the structure of the panceas, it was not until the classical experiments of von Mering and Minkowski were published in 1889 that the pancreatic theory of diabetes was placed upon a firmly established footing.

The failure of experimental attempts to produce diabetes through damming back the pancreatic juice by ligature of the ducts, or by conveying the secretion outside the body by a fistula, had led such an authority as Cohnheim to regard all pancreatic changes met with in diabetics as secondary, or accidental, complications. It was recognised, however, that the pancreas might exert an influence on carbohydrate metabolism through some other channel than its external secretion, but complete extirpation of the organ in dogs was so speedily followed by the death of the animals from shock, hæmorrhage, injury to the duodenum, or peritonitis, that no opportunity was afforded of observing the remote effects of the operation.

Martinotti, in 1888, was the first to successfully overcome these difficulties and to point out that the failure of previous experimenters might be avoided by rigid antisepsis, careful ligature of all bleeding vessels, and preservation of the vascular supply of the duodenum. It was not until the following year, however, that the

physiological relation of the pancreas to carbohydrate metabolism was conclusively proved by the publication of von Mering and Minkowski's work.

These and other observers have shown that total extirpation of the pancreas in dogs gives rise to a condition comparable in every respect to diabetes as seen in man. Usually within twenty-four hours of the operation the urine contains sugar, which gradually increases in amount until it reaches a maximum of 8 to 10 per cent. about the third day. On a diet of bread and meat a dog of 8 kilos is then found to pass from 70 to 80 grams of sugar in the twenty-four hours, and even after seven days' starvation glycosuria is still present. The amount of sugar in the urine in the latter case bears a constant ratio to the nitrogen of about 2.8 : 1, suggesting that the total quantity of sugar formed from albumin within the body is being excreted unutilised by the tissues. Although dextrose given with the food is passed in its entirety into the urine, lævulose is made use of to a fairly large extent, in contrast to what is found to be the case in diseases of the liver (Strauss). There is a marked increase in the quantity of urine passed, a dog of 7 kilos voiding from 1000 to 1200 c.c. in the twenty-four hours. Although an animal from which the pancreas has been removed eats and drinks voraciously, it rapidly wastes and loses strength, so that death takes place from inanition in about four weeks, even when lung disease, or trouble arising from the invariable disinclination of the operation wound to heal, does not bring about a fatal issue at an earlier date. When the animal is too weak to move about, the excretion of sugar begins to diminish, although food is being taken, and a few days before death it may altogether disappear, especially when there is suppurative peritonitis. Coincidentally with the fall in the excretion of sugar, acetone, diacetic acid, and β-oxybutyric acid make their appearance in the urine. When the animal is killed a few days after

the operation, the glycogen normally present in the liver and other organs is found to be absent, or only present in small amounts, unless it has been fed with lævulose in the interval, when a high percentage may be met with. Examination of the blood shows that it contains a proportion of sugar much in excess of the normal 0.1 per cent., sometimes as much as 0.4 per cent. being found, and that when the ureters are tied or the kidneys are removed the proportion is still further increased, thus pointing to the accumulation of sugar in the blood as the immediate cause of the glycosuria.

The effects of removing the pancreas have been most thoroughly and completely investigated in dogs, but analogous results have also been obtained with many other members of the vetebrate series, including cats and pigs (Minkowski and Harley), carnivorous birds (Weintraud, Kausel, and Langendorff), frogs and turtles (Aldehoff and Markuse), eels (Capparelli). The proportion of sugar in the blood has been shown, by Kausel, to be increased in herbivorous birds by removing the pancreas, but glycosuria was found to only occasionally occur, probably because the kidneys of these animals are not readily pervious to sugar. Experiments performed upon rabbits have usually been unsuccessful, because of the great technical difficulties encountered in totally extirpating the gland, but Hédon, and later Sauerbeck, have succeeded in producing atrophy and transient glycosuria by injecting oil into the duct of Wirsung, the glycosuria appearing at the earliest on the twentieth day, and being at its height from the thirtieth to the thirty-eighth day after the injection.

Partial extirpation of the pancreas may or may not give rise to diabetes, according to the amount left behind and its condition. If about a fourth or fifth of the gland is left, glycosuria only occurs if carbohydrates are present in the food ("alimentary glycosuria"). A larger por-

tion usually prevents the condition. Less generally gives rise to frank diabetes. Even when sugar does not appear in the urine after partial extirpation it will do so if the remnant is subsequently removed, and may gradually develop as the fragment atrophies. Sandmeyer found that the first trace of sugar appeared in the urine of a dog, part of whose pancreas he had removed, seven weeks after the operation, and it was not until after the lapse of thirteen and a half months that permanent diabetes developed. Death occurred eight months later. At the post-mortem a remnant weighing 0.36 gram, and showing no trace of gland structure, was found adherent to the posterior wall of the stomach, while attached to the lowest part of the duodenum was a piece of slightly changed gland-tissue the size of a pea.

The first explanation of the results of these experiments that suggests itself is that the removal of the pancreas leads to impaired digestion from absence of the pancreatic juice, and that this is in some way responsible for the onset of glycosuria. But the fact that diabetic symptoms do not supervene unless almost the entire gland has been removed is against such a theory; moreover, if the secretion of the gland is diverted, and intestinal digestion thus prevented, diabetes does not follow, although marked wasting may occur. Ligature of the pancreatic duct likewise fails to give rise to glycosuria, as a rule.

Disease of the solar plexus has been regarded by some as a cause of the diabetes, and, as the plexus is almost unavoidably injured in the removal of the pancreas, this might possibly be the explanation of the symptoms caused by the depancreatisation of animals. It was shown by Minkowski, however, that if the descending portion of the gland is transplanted into the subcutaneous tissue of the abdominal wall, and allowed to become engrafted there, the intra-abdominal portion can be removed, after the graft has been severed from all its nervous connections, without

producing diabetes, but that if the graft is subsequently removed—or atrophies—diabetes develops.

The cause of the glycosuria, and of the accumulation of sugar in the blood, appears therefore to be dependent upon some influence which the pancreas exerts by way of the blood or lymph stream. There are two possible means by which this can be effected: first, it may be that the cells of the pancreas normally destroy, or modify, some toxic substance, produced in other parts of the body, which interferes with the utilisation of sugar by the tissues; or, secondly, that the pancreas produces an internal secretion which is necessary for the splitting up and use of sugar by the other cells of the organism.

The first, or *auto-intoxication, theory* is that which was originally favoured by Minkowski, but it was later abandoned by him in favour of the second hypothesis. Bosanquet, in his Goulstonian lectures, favours the view that diabetes, is due to an increased internal dissociation of tissue (possibly fat) into sugar, caused by a toxic substance that is produced in the course of normal metabolism, and which is normally neutralised by the pancreas. He points out that poisonous doses of phloridzin, diuretin, and uranium nitrate give rise to glycosuria, and that suprarenal extract and other reducing substances, when applied directly to the pancreas, produce a similar effect. That it is not necessary for the bulk of the blood to come into actual contact with the pancreatic cells to prevent hyperglycæmia and glycosuria is suggested by the restraining effect of even a small proportion of the pancreatic tissue, and by the results of grafting a portion of the gland into the abdominal wall, for under such conditions only a small fraction can be directly influenced by the gland cells. It is possible, however, that when only a small part of the pancreas is left in an experimental partial extirpation of the gland, a sufficient amount of an internal secretion may pass into the blood stream to neutralise any toxic substance

that may be present there. Tuckett has suggested that the pancreas normally forms such an internal secretion, which enters the circulation by way of the thoracic duct, and there neutralises a toxine absorbed by the lymphatics from the intestine during digestion. In support of his hypothesis he states that if the thoracic lymph from a fasting dog is injected into the portal circulation of a cat, no hyperglycæmia or glycosuria results; but that if the lymph from a dog during digestion is similarly injected, a hyperglycæmia, varying from 0.3 to 0.9 per cent., and a glycosuria, varying from 1.0 to 9.0 per cent., are produced. Confirmation of his results is, however, as yet lacking. Minkowski has shown that if the efferent vessels from a pancreatic graft are ligatured, so as to ensure that all the returning blood is passed into the general circulation, diabetes does not develop, thus demonstrating that the transmission of the efferent blood into the portal circulation is not necessary to prevent the onset of glycosuria. As the result of experiments upon dogs Lorand has recently stated that there is a relation between the islands of Langerhans and the thyroid, the former secreting a substance which neutralises a poison produced by the latter, and that diabetes may arise either from increased functional activity of the thyroid or from failure of the cell islets to perform their function.

The theory that the blood normally contains a *sugar-splitting ferment*, which is absent in diabetes, was warmly advocated by Lépine, who stated that the blood of diabetics has a diminished capacity for transforming sugar. Crofton, who supported Lépine's observations, claimed to have isolated the ferment by which glycolysis is brought about, and to have identified it with trypsin. Other observers have found, however, that when precautions are taken to prevent contamination, normal blood possesses no glycolytic power, and have regarded the positive results as being due to the action of micro-organisms.

Indeed, Lépine himself subsequently gave up the idea that glycolysis occurs in the blood, and referred it to the tissue cells.

Blumenthal and others have asserted that the cells from the pancreas, liver, spleen, muscle, etc., possess a strong glycolytic power; which is much increased if pancreatic extract be mixed with the cell juice from other organs. Giacco found that this power varied in different organs, being great in the heart and little in the pancreas itself. He also stated that it was not a vital phenomenon, for it persisted after the tissues had been boiled. According to Umber, however, when careful precautions are taken against contamination with micro-organisms, the tissues outside the body exhibit only very slight glycolytic powers. The same observer also found that the sugar-splitting power of the blood was not greater in the pancreatic vein than in the general arterial or venous systems, as it would have been if the pancreas secreted a sugar-destroying substance.

An explanation of the phenomena of glycolysis on the lines of Ehrlich's "side-chain" theory has been advanced by Cohnheim, for he found that expressed muscle juice is inactive to sugar until it has been mixed with expressed tissue juice from the pancreas, or with an ether precipitate from it. From this he argues that the muscle produces a ferment which is itself incapable of decomposing sugar, but which, when acted on by an "activator substance" derived from the pancreas, gains that power, in much the same way as a complement and amboceptor are necessary for hæmolysis and analogous processes. The presence of blood in the muscle was found to cause glycolysis without the addition of pancreatic extract, indicating that the activator substance derived from the pancreas was present in the blood. This substance Cohnheim states is soluble in water and alcohol, but is insoluble in ether, and, since it is not destroyed by boiling, he concludes that it is not a

ferment, but analogous to adrenalin, iodothyrin, secretin, and other products of internal secretion. Cohnheim's methods and conclusions have been criticised by Claus and Embden, who were unable to confirm his results, but the main fact that the pancreas gives rise to an activator substance for a glycolytic enzyme produced by other tissues of the body appears to have since been firmly established. Experiments have been conducted by Pavy which point to a "co-ferment-like, or activator substance," being yielded by the pancreas, which aids in the synthetic process concerned in the linking-on of sugar in the construction of proteid, and the absence of which would lead to failure of carbohydrate assimilation and the condition met with in diabetes.

There is little or no doubt that the *nervous system* plays a part in the production of some forms of diabetes, and, although the experiments already detailed show that injury of the nerves in the neighbourhood of the pancreas is not responsible for the symptoms caused by extirpation of the gland, it is possible that indirectly the nutrition of the nerve centres may be influenced in such a way as to produce metabolic changes in the pancreas and other tissues of the body. There is, however, no experimental work to support such a view, and it is now generally admitted that the most satisfactory explanation of pancreatic diabetes is that which supposes that the disease is due to the absence of some ferment, or co-ferment-like body, which normally reaches the blood from the gland.

Injury or rough handling of the pancreas, painting it with piperidine, nicotine, coniine, pyridine, adrenalin, etc., are said to give rise to *transitory glycosuria*. This subject has been recently re-investigated by Underhill, who found that "insults" of the gland, by freezing with ethyl chloride or rough handling, caused neither hyperglycæmia nor glycosuria, but that the application of the drugs referred to gave rise to both. Further investigation showed,

however, that suppression of the respiratory process, to the point of dyspnœa, caused an increase of sugar in the blood which could be prevented by the administration of oxygen, and that a similar use of oxygen also prevented the hyperglycæmia generally following the application of piperidine and all the other substances mentioned, except adrenalin, so that they appeared to act through the blood upon the respiratory centre. The action of adrenalin appeared, however, to be directly upon the pancreas, and was unique in this respect.

The view has been held by some authors that diabetes is *an infectious disorder*, and since, as we have already seen, changes may be brought about in the structure of the pancreas by the action of micro-organisms and their toxines, it is not impossible that, at least in some instances, a microbic infection may give rise to the disease. Hammarschlag and Kauffmann have, indeed, succeeded in producing glycosuria by feeding animals upon bacteria obtained from the intestines of diabetics, and by injecting them intravenously, but evidence that it was a true diabetes is lacking, and there is no proof that the infection was specific.

The *first recorded case* in which disease of the pancreas was noticed to be associated with diabetes was described by Cowley in 1788. In this the gland was found to be atrophied and to contain calculi in its ducts. Chopart described a similar case in 1821, and Bright, in 1833, gave an account of a diabetic, nineteen years of age, with jaundice and fatty stools, the head of whose pancreas was found at the post-mortem to be converted into a hard, nodular tumour, firmly adherent to the duodenum. Subsequently other cases were published by Elliotson, Frerichs, Hartsen, Fles, von Recklinghausen, Munk, Silver, and Bouchardat, but the first to definitely propound the theory of pancreatic diabetes was Lancereaux, in 1877. He claimed that diabetes, accompanied by wasting

("diabéte maigre"), was due to disease of the pancreas, while that in which there was no marked loss of flesh ("diabéte gras") arose from some other cause. The pancreatic type of the disease, he believed, was also characterised by the brusqueness of its onset, the gravity of the symptoms, and the rapid progress of the disease. Subsequent observation has not confirmed the clinical distinctions thus drawn by Lancereaux; in fact, many cases of glycosuria, of undoubted pancreatic origin, are of insidious onset, progress but slowly, and show no marked loss of flesh. We have had the opportunity of observing several cases in which glycosuria has developed after operations for gall-stones, or disease of the pancreas, and have been much struck by the slow progress of the disease and generally good condition of the patient, even after the lapse of several years. One patient who was operated on twelve years ago for gall-stones was found to have glycosuria eight and a half years after the operation, and still passes a considerable amount of sugar in the urine, but enjoys good general health. In another and similar case the glycosuria has persisted for six years, and in a third case of cholelithiasis associated with glycosuria, in which we have repeatedly had the opportunity of examining the urine, the patient was said to be alive and well, except for some local irritation due to the sugar, five years after the operation and the discovery of the glycosuria.

It it now generally acknowledged that the character of the symptoms affords no clue as to the pancreatic or non-pancreatic origin of the disease, and that attempts to make a clinical distinction are usually unsuccessful, except in those instances where a history of past disease of the pancreas affords an indication. It is impossible, therefore, to judge from bedside experience how far pancreatic disease is responsible for diabetes in man. On turning to post-mortem records for information on this

point, we are at once confronted by the divergent experience of different observers. Windle reported that in one hundred and thirty-nine cases of diabetes the pancreas was diseased in seventy-four (53 per cent.). Seegen analysed the records of ninety-two cases and found a pancreatic lesion in seventeen (19 per cent.). Frerichs in forty-four cases found disease of the pancreas in sixteen (36 per cent.). Out of fifty-four cases of diabetes, examined in the Berlin Pathological Institute, Hansemann reports that there was a lesion of the pancreas in forty (17 per cent.). Bloch, quoted by Oser, collected twenty-two cases, from the records of the Vienna General Hospital, in twelve (55 per cent.) of which the pancreas had been recognised as abnormal. Williamson examined twenty-three cases and in fifteen (65 per cent.) found evidence of pancreatic disease. Opie investigated the pancreas in nineteen cases of diabetes and detected some abnormality of the gland in fifteen (79 per cent). Bosanquet records nineteen cases, in seventeen (90 per cent.) of which there was disease of the pancreas.

These different results are no doubt to a great extent dependent upon a divergence of opinion as to what may be regarded as normal and what as pathological when examining the pancreas in the post-mortem room, and also to the use of the microscope by modern observers as an aid to diagnosis in some instances. Opie, who made a histological examination of the gland in the nineteen cases he investigated, found evidence of disease in all but four (21 per cent.), whereas Seegen, out of his ninety-two cases, states that the organ was normal in seventy-five (81 per cent.); in four of Opie's cases, however, no gross abnormality could be detected, and it was not until they were submitted to microscopical investigation that a lesion was discovered. The statistics of the older observers, not based upon careful macroscopical and microscopical examination, are therefore probably of little value, and,

as the number of instances in which such investigations have been performed is as yet too small to allow of any reliable inference being drawn, no definite answer can be given to the question as to what proportion of cases of diabetes are due to disease of the pancreas? Opie considers that in considerably more than half the disease results from a destructive lesion of the gland, while Bosanquet thinks that "it is becoming increasingly probable that the pancreas is diseased in all cases of diabetes mellitus."

On attempting to determine from published reports the relative frequency in diabetes of the various diseases to which the pancreas is liable, the difficulty of reconciling the results obtained by different investigators is again encountered. According to the older observers, the most common lesion is *atrophy* of the gland. Windle found it in over 59 per cent. of the cases he investigated and Frerichs in 75 per cent. The statistics, quoted by Hansemann, from the Berlin hospitals in the space of ten years, show forty cases of diabetes with disease of the pancreas, in thirty-six (90 per cent.) of which there was simple atrophy, and in three (8 per cent.) atrophy and sclerosis. The more recent observations of Williamson and Opie, however, give much lower figures, the former finding simple atrophy in four out of eleven cases (27 per cent.), and the latter in four out of fifteen (26 per cent.). Some explanation of this difference is afforded by the more careful and exact methods of investigation employed in recent years, and there is no doubt that in the past too great a reliance upon the naked-eye characters caused many cases in which the size of the pancreas appeared diminished to be classified as simple atrophy, which were, in reality, examples of the atrophic changes resulting from chronic inflammation of the gland. The form of atrophy which Hansemann considered was always associated with diabetes appears to belong to this class, and

although there is no means of determining whether the atrophy of the pancreatic cells leads to the increase of fibrous tissue, or the fibrosis results from inflammatory changes in the gland, and then, by its contraction, produces alterations in the glandular acini, it is now generally considered that the fibrosis is the principal lesion, and the cell atrophy a minor phenomenon. Simple atrophy, therefore, although it may be the only lesion found in some cases of diabetes, would not appear to play such an important part in the production of the disease as was at one time supposed, and there is no evidence to show that the pancreas is liable to a particular form of atrophy which invariably gives rise to diabetes.

In a few cases of diabetes *fatty degeneration* of the pancreas has been found, after death, as the only discoverable lesion. Bosanquet met with a recognisable degree of fatty change in ten out of one hundred cases, which, in three, was combined with some fibrosis. Williamson in his series met with one case of lipomatosis, in which there was atrophy and fatty degeneration, and one where, besides atrophy and fatty degeneration, there were evidences of inflammatory changes.

The earliest recorded case in which disease of the pancreas was recognised as being associated with diabetes was, as we have seen, one of *pancreatic calculi*. But as Hansemann was only able to find fourteen instances in seventy-two cases (19 per cent.) collected from medical literature, and Oser quotes but twenty-four examples in one hundred and eighty-eight cases of diabetes (14 per cent.), the association is not a very common one, particularly as the lesion is so obvious that it would not be readily overlooked. The mere presence of calculi cannot be regarded as directly responsible for the diabetes, for blocking of the ducts, by ligature or otherwise, has been proved not to cause glycosuria; it is to the fibrotic changes accompanying them that we must look for the explanation.

That this is the true cause is shown by the fact that diabetes is only found in those cases where there is very marked overgrowth of fibrous tissue, whereas in those instances where the concretions are not associated with advanced interstitial changes glycosuria does not occur.

In a similar way, although *cysts* of the pancreas have been found in from 5 per cent. (Oser) to 7 per cent. (Dieckhoff) of diabetics showing a pancreatic lesion, there are many cases of cysts in which glycosuria does not occur. In some instances sugar may appear in the urine some time after a cyst has been recognised and surgically treated, owing probably to the advance of the chronic inflammatory changes to which the formation of the cyst was originally due.

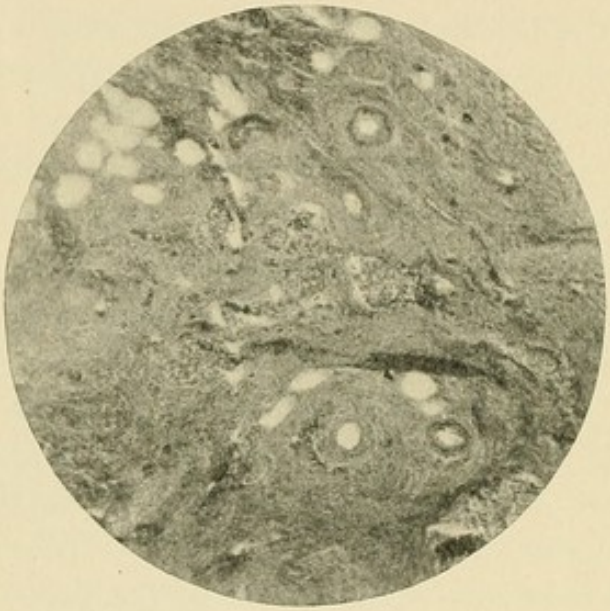


Fig. 105.—Fibrosis of the pancreas, from a case of diabetes associated with the presence of pancreatic calculi (× 32).

We have had the opportunity of investigating a case of this description through the kindness of Dr. Churton, under whose care it came at the General Infirmary, Leeds. The patient was operated on by one of us in June, 1896, for a cyst of the pancreas. The urine was then free from sugar and showed no other abnormality, save that it gave a well-marked "pancreatic" reaction. In February, 1905, we heard that the patient had been admitted to the Infirmary suffering from diabetes, and, by the courtesy of the house physician, we were able to obtain a twenty-four hour sample of the

urine and a specimen of the fæces. The former measured 62 ounces, was strongly acid in reaction, specific gravity 1.030. There was no albumin, but a well-marked reaction for nucleo-proteid was obtained. Acetone was absent, but there was a trace of diacetic acid. No reaction for bile-pigment, urobilin, or indican was obtained. The urine reduced Fehling's solution and gave a characteristic reaction with phenylhydrazin. Titration with Fehling's solution showed 4.5 per cent. of sugar (80 grams in the twenty-four hours). No indication of the presence of a pentose could be found. The total nitrogen, urea, uric acid, chlorides, phosphates, sulphates, and oxalates were estimated, and found to be normal, except that the oxalates showed an excess (0.32 gram in the twenty-four hours). The "pancreatic" reaction gave many fine crystals, soluble in 33 per cent. sulphuric acid in ten to fifteen seconds. The fæces were of a light yellow colour and faintly alkaline in reaction. They gave a well-marked reaction for stercobilin. There was no marked excess of unabsorbed fat, but the normal relation between the "neutral fats" and "fatty acids" was disturbed, the former constituting 15 per cent. and the latter only 5 per cent. of the dry weight of the fæces, thus indicating some interference with the digestive functions of the pancreas.

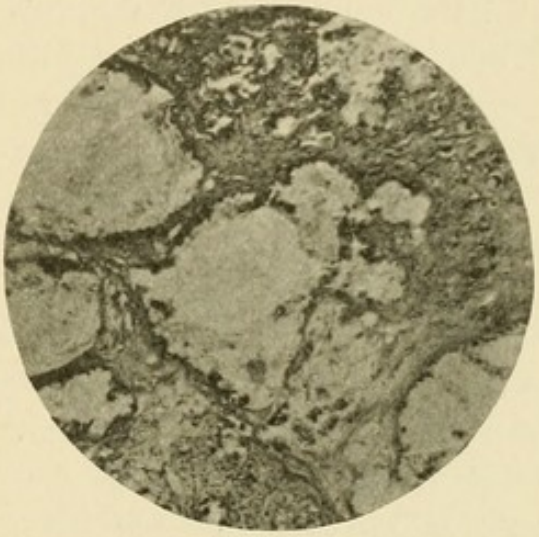


Fig. 106.—Columnar-celled carcinoma of the pancreas undergoing colloid change, from a case of diabetes (× 50).

The association of *cancer* of the pancreas with diabetes is relatively uncommon. Windle found it in 4 per cent.

of his cases; Frerichs in 6 per cent., Dieckhoff in 7 per cent., and Williamson once in his series of twenty-three consecutive cases. Glycosuria has been met with in only two of the forty cases of primary malignant disease of the pancreas in which we have had the opportunity of examining the urine, and once where the gland was involved in a secondary growth. The last is of particular interest from several points of view, for it demonstrates in a very striking manner the importance of the pancreas in carbohydrate metabolism in the human subject, and also the value of the "pancreatic" reaction in diagnosis. When the patient was first seen, early in December, 1905, there was an abdominal tumour which it was thought might be pancreatic, but a specimen of urine on being submitted for examination gave no "pancreatic" reaction and was free from sugar. On opening the abdomen the tumour was found to be due to a growth in the first part of the duodenum, and a gastro-enterostomy was therefore performed. On the 18th of January a second specimen of urine was examined, and, although it was still free from sugar, it was found to give a well-marked and characteristic "pancreatic" reaction, suggesting that the pancreas had now become involved in the growth. At the request of the friends, the abdomen was again opened, and it was seen that the growth had invaded the pancreas and was beginning to involve the common bile-duct. As it was impossible to attempt the removal of the tumour, a cholecystenterostomy was performed. In May, 1906, the urine was again examined, and was found to contain 5.25 per cent. of sugar; a month later this had increased to 7.0 per cent.; in July it had reached 7.25 per cent.; in August, 7.5 per cent.; and in October, 9.5 per cent. was present. In spite of the high percentage of sugar in the urine the general condition of the patient remained fairly good and she complained of no other symptoms than thirst and a voracious appetite. Considerable

quantities of acetone and diacetic acid were present in the urine in May, but with careful treatment they gradually diminished in amount, until in the early part of October only traces could be detected. Toward the end of October the gall-bladder was found to be distended and a few days later jaundice developed. The patient died deeply jaundiced on November 5, 1906.

In some cases of malignant disease of the pancreas glycosuria has appeared as an early symptom, which has later disappeared, while in others it has only been met with towards the termination of the disease. The temporary appearance of sugar in the urine in these cases is possibly dependent upon the disturbance in the functions of the gland, caused by an inflammatory reaction attendant upon the spread of the growth, which subsequently quiets down, leaving sufficient unaltered tissue to carry on the work of carbohydrate metabolism. In a case of this description under Macaigni, quoted by Oser, there was transient glycosuria for seven months, then eleven months' cachexia without glycosuria. Death took place twenty-three months after the onset of the disease. Post-mortem a large, very hard cancer of the head of the pancreas, replacing one-half of the gland, was found. The rest of the organ appeared to be normal. It has also to be borne in mind that where a portion of the pancreas has been destroyed by growth the condition resembles that produced in animals by partial extirpation of the gland, so that if carbohydrates are excluded from the diet the alimentary glycosuria, which previously existed, may disappear. In most recorded cases where sugar has appeared in the urine as a terminal symptom either the whole organ has been replaced by a mass of growth, or the portions that have remained have undergone sclerotic changes, so that no normal pancreatic tissue was left to carry on the functions of the gland.

The absence of permanent diabetes in most cases of

cancer of the pancreas is due to the growth being limited in many instances to one portion of the gland, usually the head. In about 29 per cent. of cases, however, this explanation will not hold good, for in that proportion there is a diffuse growth affecting the whole organ. It is supposed that in these cases either the tumour cells possess a glycolytic power, or the new-growth insinuates itself between the pancreatic cells in such a way as to obliterate the normal structure of the gland without destroying it entirely. That such a process of growth is possible is shown by the presence in some instances of unaltered island of Langerhans in the midst of the cancerous material, while in support of the former hypothesis Hansemann points out that in primary carcinoma of the suprarenals Addison's disease is rare.

When considering the general pathology of the pancreas, we pointed out that the commonest of all lesions to which the organ is liable are those of an inflammatory nature, although until recently they have failed to receive, both from clinicians and pathologists, that recognition which their importance deserves. The association of diabetes with *inflammatory changes, and their sequelæ*, have in a similar way been largely overlooked, or the disease has been referred to some other cause. As we have seen, the special form of atrophy described by Hansemann is in reality a fibrosis due to inflammatory changes in the gland; calculi and cysts are also probably not responsible for the glycosuria with which they are associated, but occur in the course of a chronic inflammation which ultimately destroys the structure of the gland, and some cases, at least, of diabetes associated with malignant disease of the pancreas are caused by the changes brought about by secondary inflammation. Dieckhoff in his analysis of fifty-three cases found acute pancreatitis in 10 per cent. and chronic pancreatitis in 36 per cent. Williamson met with four instances of cirrhosis of the pancreas in twenty-three

cases, and Opie with four of chronic inflammation in nineteen cases, so that it is probable that inflammatory changes play a not unimportant part in the production of the disease, especially if the different manifestations to which reference has been made are taken into account.

Acute pancreatitis is not itself a common disease, and is for this reason alone not frequently met with as a cause of diabetes. In the one hundred and eighty-eight cases collected by Oser there were three in which diabetes was associated with hæmorrhage into the pancreas, three of necrosis of the gland, and six of abscess; yet in about one hundred cases of acute inflammation, collected by Fitz and by Seitz, diabetes was only present in two. The reason for the comparative rarity with which glycosuria occurs in acute pancreatitis appears to be that when the whole organ is destroyed death usually follows very rapidly, and when the progress of the disease is less acute portions of the gland are left unaffected. The experiments of Guleke on dogs have shown that, when complete necrosis of the pancreas has been induced, by injecting oil into the ligatured pancreatic duct, glycosuria always occurs, but that when a portion of the pancreas has been left intact no sugar can be found in the urine. This observer also found that in animals where chronic pancreatitis had been produced by the same means glycosuria was present in some and not in others.

A case of hæmorrhage into the pancreas, causing destruction of the whole gland, and associated with the appearance of sugar in the urine, is described by Bosanquet in his Goulstonian lectures. The patient, a laundress aged fifty-three, was admitted into Charing Cross Hospital, under the care of Dr. J. M. Bruce, on January 24, 1893. A week before she had been seized with pain in the abdomen, which rapidly swelled and became hard to the touch. She had previously had no symptoms of diabetes, but then complained of thirst, and on examining the urine it was found

to contain from 10.12 to 11.25 grains of sugar in the twenty-four hours. Her temperature, which on the 24th was 100° F., gradually rose, and on the 29th and 30th she had rigors. On the latter day acetone was present in the urine. Finally she died in collapse without any appearance of coma. At the necropsy the layers of the mesentery were everywhere separated by a large mass of disintegrated blood-clot and blood-stained fluid. The stomach was adherent to the left lobe of the liver, and, on separating the two, several pints of blood-stained grumous fluid escaped. In the situation of the pancreas was a breaking-down mass of tissue, along with much bloody fluid. There was also diffuse fat necrosis and evidence of recent peritonitis. Such a case constitutes a natural experiment on the removal of the pancreas in a human being, and, as Bosanquet points out, the results exactly correspond to those obtained in animals.

An example of the association of glycosuria with acute pancreatitis in which recovery took place has been recorded by Gifford Nash, in the "Lancet" of November 11, 1902. The patient was a man of sixty, who for seven years had suffered from "bilious attacks" and discomfort at the pit of the stomach. On October 27, 1901, he was seized with sudden pain in the abdomen. There was no jaundice, and the symptoms suggested intestinal obstruction. The urine was increased in amount, and contained, on November 5th, 8.75 grains of sugar to the ounce. Operation was undertaken on November 17th. The pancreas was found to be enlarged, there was fat necrosis in the neighbourhood of the gland, and a large calculus was found in the gall-bladder. Cholecystotomy was performed and the patient slowly recovered. On December 28th the urine contained 4.5 grains of sugar per ounce; on March 1st, 1902, 4.5 grains also, but on May 17th the glycosuria had disappeared. Through the kindness of Dr. Gifford Nash and Dr. J. Tait, we were

able to examine a specimen of the patient's urine in November, 1902, and found that the glycosuria had returned. A well-marked "pancreatic" reaction was also obtained. A second specimen, examined on February 2, 1904, gave similar results. It was then stated that the patient was in very good health, and had had no illness since the operation. In January, 1906, a further examination was made, and the urine was found to contain 0.95 per cent. of sugar. No acetone or diacetic acid was present, but it still gave a positive "pancreatic" reaction.

Chronic interstitial pancreatitis has been frequently observed in association with diabetes, but in the majority of cases where interstitial changes in the pancreas arise from obstruction of the ducts by gall-stones, or from other causes, glycosuria is not met with as a symptom. In sixty-five consecutive cases, where biliary calculi were found in the common duct at operation and the pancreas was enlarged and hard, we have detected sugar in the urine of four (16 per cent.). In three of these the amount was under 0.2 per cent., and in the fourth 0.4 per cent. was present. After operation the sugar disappeared from the urine in all but the last, in which it slowly increased in amount, the patient dying from diabetic coma ten months subsequently. Since the interstitial changes arising from the presence of gall-stones in the common duct principally affect the head of the gland in the first

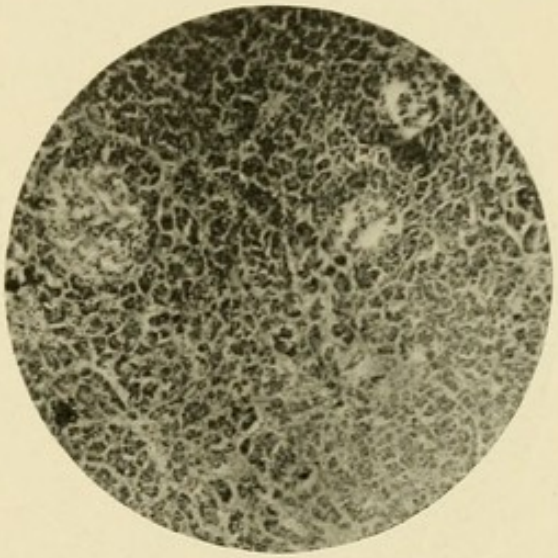


Fig. 107.—Spheroidal-celled carcinoma of the pancreas, islands of Langerhans not affected, no glycosuria (× 40).

instance, and the results of experiments upon animals have shown that even a small portion of healthy pancreatic tissue will prevent the onset of diabetes, or at least delay the appearance of the symptoms, so long as it remains undestroyed by fibrotic changes, the comparative

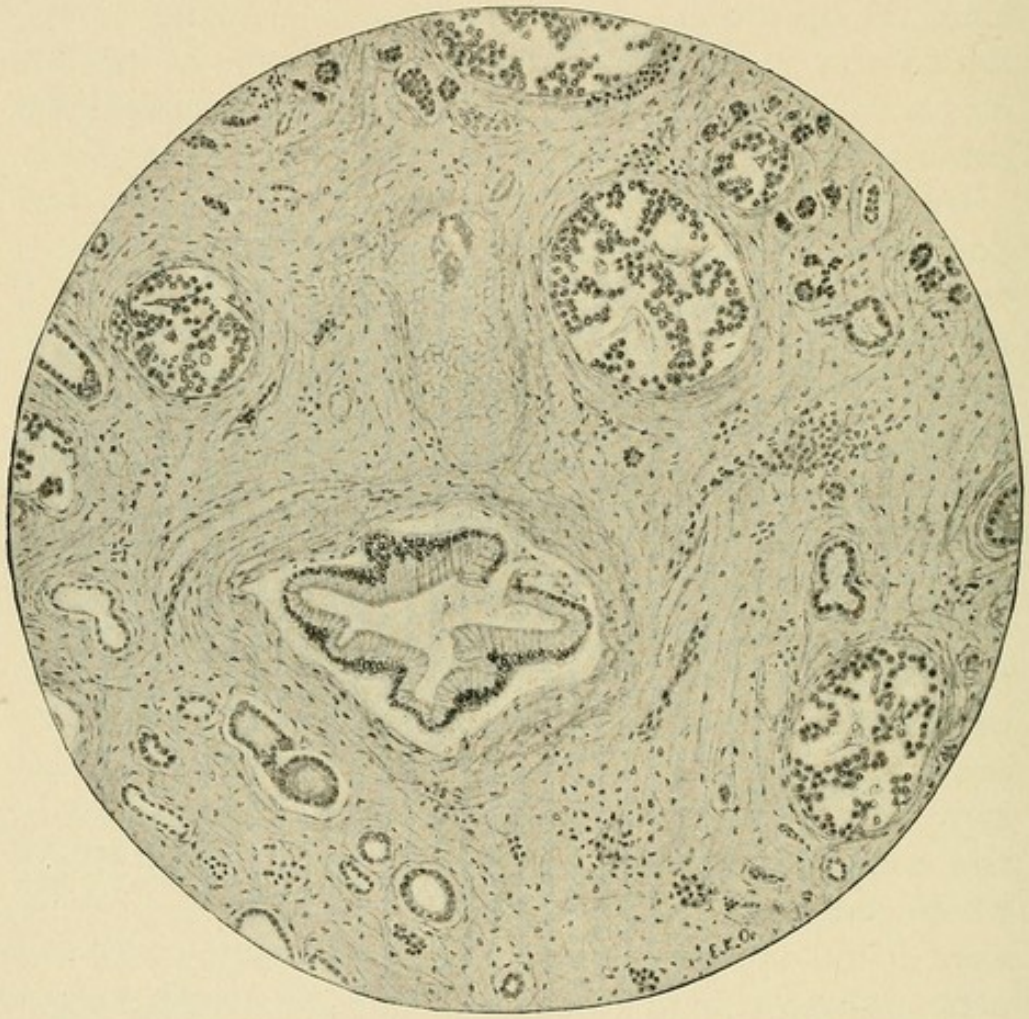


Fig. 108.—Chronic interstitial pancreatitis following duct obstruction, from carcinoma of the duodenum, showing islands of Langerhans unchanged though embedded in sclerotic tissue; no glycosuria (Opie).

rarity of glycosuria in these cases is not difficult to explain. When, however, a great part of the parenchyma has been destroyed, or is functionally impaired, by the progressive changes consequent on repeated or long-continued irritation, either from gall-stones or an unre-

lieved duodenal catarrh, sugar will make its appearance in the urine, first as an alimentary glycosuria, and later as a permanent diabetes.

Fig. 109.—Section of the pancreas from a case of diabetes following gall-stone obstruction (× 42).

Some observers have attempted to define a particular type of pancreatitis associated with diabetes. Hoppe-Seyler and Fleiner have described cases of the disease accompanying general arterial sclerosis, and Bosanquet in two out of seven cases he investigated found arteriosclerosis, accompanied, in one instance in which the glycosuria had been intermittent, by gangrene of the leg. Bosanquet suggests that in the last mentioned case the appearance and disappearance of the sugar might be due to intermittent pancreatic failure, analogous to the "intermittent claudication" sometimes met with in arteriosclerosis. Lemoine and Lannois thought that the new-growth of fibrous tissue originated in the perivascular tissue, whence it spreads into the parenchyma. In four cases they

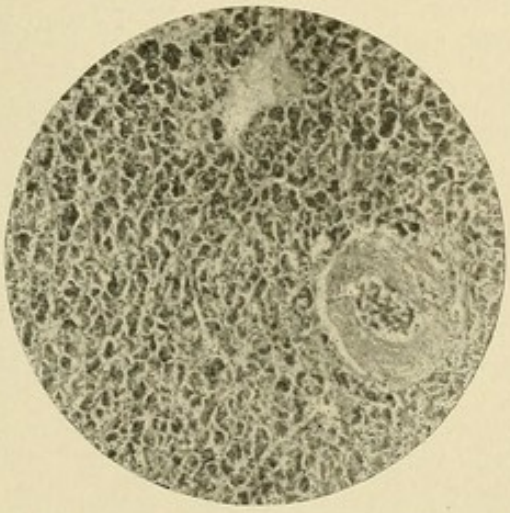


Fig. 110.—Chronic interstitial pancreatitis with arteriosclerosis, from a case of diabetes (× 40).

examined, they described the penetration of fibrous bands into the acini, separating the cells and giving rise to a unicellular sclerosis.

Opie considers that diabetes is peculiarly related to *interacinar pancreatitis* and that in the interlobular form it is rare. The difference, he considers, depends upon the relation of the fibrous tissue overgrowth to the islands of Langerhans, which he, in common with many other observers, believes are responsible for the elaboration of the internal secretion by means of which the pancreas exerts its influence upon carbohydrate metabolism. The newly formed fibrous tissue in interacinar pancreatitis is diffusely distributed within the lobules and between the individual acini, so that the islands are affected at the same time as the other elements of the gland, but in the interlobular form, which is the type following duct-obstruction, the proliferation of fibrous tissue takes place between the lobules and invades them from the periphery, so that the cell islets suffer only when the process is far advanced, and the secreting parenchyma has been replaced by masses of scar-like tissue. Opie found that diabetes was present in seven out of nine cases of interacinous pancreatitis, but that in only one out of twenty-one cases of chronic interlobular inflammation of the gland was there sugar in the urine. In this one case of interlobular inflammation the induration of the gland was far advanced and the islands of Langerhans were fibroid. The two cases of interacinous pancreatitis in which diabetes was absent were both, he found, in an early stage of the disease.

The suggestion that the *islands of Langerhans* are concerned in the production of the "internal secretion" of the pancreas was first made by Laguesse. This view was subsequently adopted by Schäfer, Diamare, and others. The theory that such a relationship exists is based partly on histological grounds, and partly upon the

results of experimental work, but the most important evidence in support of it has been furnished by pathological observations, which suggest that pancreatic diabetes is due to a disturbance of the functions of the cell islets. The peculiarity of their structure, their independence of the duct system of the gland, and their comparative resistance to certain morbid changes by which the secreting acini are destroyed, point to their being independent organs with an independent function; while their rich blood supply may be taken to indicate that they are possibly vascular glands, engaged in the elaboration of some internal secretion which is poured into the blood stream. Ssobolew, who has sought by experimental means to prove the relationship of the islands of Langerhans to carbohydrate metabolism, states that when animals are overfed with carbohydrates the granules, which have appeared in the cells during hunger, diminish in number, in the same way as the zymogen granules of the secreting cells diminish as the result of functional activity. Intravenous injections of sugar, he believes, bring about a similar result. But this has been denied by Schmidt, who also failed to observe any change on introducing sugar into the peritoneal cavity of mice and guinea-pigs. Schulze, however, experimenting with guinea-pigs, has confirmed the observations made by Ssobolew.

Basing her experiments upon the observation of Schulze, Ssobolew and others, that complete atrophy of the glandular acini of the pancreas is caused by ligaturing the duct, while the islands of Langerhans remain unchanged, Lydia De Witt has attempted to isolate the cell islets in cats, and study the physiological action of an extract made from them. She found that the changes in the glandular parenchyma were much the same as those described by Ssobolew, but that when no special effort was made to avoid including the blood-vessels in

the ligature, the islands, as well as the gland tissue, sometimes atrophied, whereas when precautions were taken to avoid interfering with the blood supply of the gland the islands were well preserved, regardless of the extent of atrophy of the gland tissue. No sugar was found in the urine, either after the operation or just before death, but in three out of four cases a positive "pancreatic" reaction was obtained when the urine was examined shortly before the animal died. To test the physiological powers of the atrophied gland, it was removed immediately after death, extracted with glycerine or water, and the digestive and glycolytic actions of the extracts investigated. In seven out of twenty cases there was no digestion of starch, fibrin, or fat, while in several others the digestive action was very much weakened, the diminution and absence of digestive action being apparently proportionate to the degree of atrophy of the glandular tissue. No appreciable weakening of the glycolytic, or activator, power of the extract, as tested by Cohnheim's method, was noticed in any of the cases, even when the glandular tissue had undergone atrophic changes. The results of these experiments, although suggestive, and tending to support the theory that the islands of Langerhans manufacture a substance analogous to the "activator principle" of Cohnheim which favours the glycolytic action of muscle ferment, were not as decisive as had been hoped, for the isolation of the islands was not always complete, and it was found difficult to obtain from the cat's pancreas sufficient extract to make many satisfactory tests.

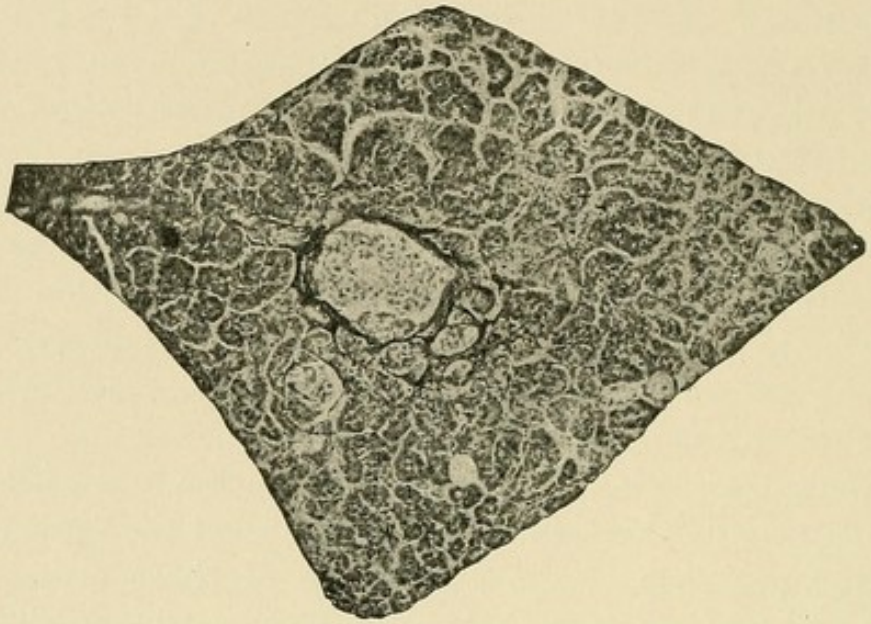
Rennie has carried out some investigations with extracts prepared from the large cell islets, dissected out free from pancreatic tissue, met with in Lophius piscatorius and Scorpœna scropha, and found that they had no inverting power. Diamare and Kuliabko state, however, that some inversion takes place on standing for forty-

eight hours. The latter have also shown that the extract has no digestive power for starch, whereas an extract made from the pancreas of the same fish rapidly converts starch into sugar.

The *pathological changes that have been met with in the interacinar islets* in cases of diabetes are hyaline degeneration, necrosis, atrophy with vacuolisation and liquefaction of the cell-protoplasm, acute and chronic inflammation with hæmorrhage, sclerosis, or calcification, and diminution of the number of islets.

Opie's description of hyaline degeneration in the islands of Langerhans alone, in diabetes, furnished the most convincing evidence of the association of these structures with carbohydrate metabolism up to that time available, and from the publication of his paper in 1901 may be dated a revival of interest in the pancreatic theory of diabetes, and a more searching and minute inquiry on the part of other observers into the condition of the cell islets in fatal cases coming to post-mortem. In nineteen cases of diabetes, in which Opie investigated the condition of the islands of Langerhans, he found hyaline degeneration in seven (35 per cent.). The first example of the lesion that came under his observation was in a severe case of diabetes. The islands were so completely altered as to be unrecognisable, and the secreting parenchyma was also in great part destroyed. In subsequent cases of his series the relationship of the diabetes to the lesion in the islands was more conclusively demonstrated, for, although these structures had undergone very grave alterations, and were often converted into almost homogeneous masses of hyaline material, the secreting parenchyma showed in some instances only insignificant changes, and in parts of the gland was unchanged.

Other observers, including Wright and Joslin (two cases with only very slight alterations of the glandular acini), Herzog (one with slight chronic interstitial inflammation),



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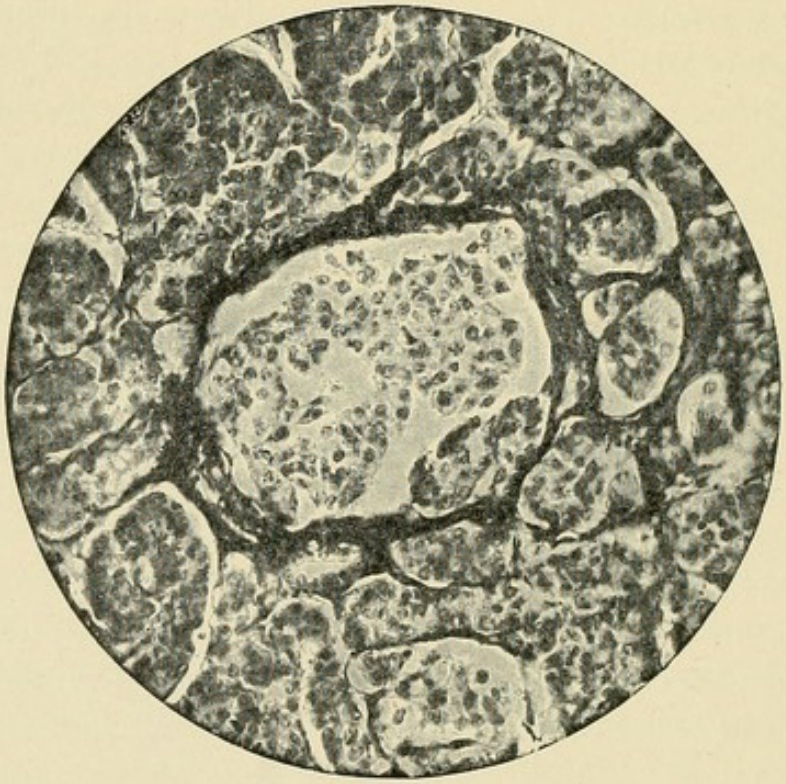

b

Fig. 111.—Sections of the pancreas from a case of diabetes showing sclerosis of the capsule of the islands of Langerhans: *a*, Low power; *b*, the same islet under higher magnification (Gaylord and Aschoff).

Schmidt (one with no lesion of the parenchyma), and Lépine (one with recent fibrosis), have met with a similar condition, but it would not appear to be as common as Opie's experience would suggest. Bosanquet has pointed out that the possibility of the degeneration being a secondary change in diabetes has not been excluded. He quotes a case in which he found it apart from diabetes in association with extensive arteriosclerosis of the pancreatic vessels, in a woman who died after an operation for gall-stones.

According to Weichselbaum and Stangl, who have studied the islands of Langerhans in thirty-five cases of diabetes, the lesion most frequently met with is simple atrophy of the cells together with vacuolisation and liquefaction of the cell-protoplasm. Sclerosis of the cell islets was only met with in four out of their second series of seventeen cases. Herzog has studied three cases of diabetes in which the islands were the seat of marked sclerotic changes, and Schmidt has met with two in which there was interacinar pancreatitis so seriously involving the cell islets that many of them were converted into connective-tissue balls resembling fibrosed glomeruli, as they were also in one of Herzog's cases. In a case reported by Lépine the islands were surrounded, and in places partly destroyed, by a new-growth of fibrous tissue. Gentes has also described a case of diabetes with chronic interstitial pancreatitis invading the islands of Langerhans. An acute inflammation, limited to the cell islets, was met with by Schmidt in the case of a child of ten whose urine contained 6.8 per cent. of sugar, and focal necrosis of the pancreas involving the islands of Langerhans was seen by Opie in one case.

Absence of the islands, or diminution of their number, has been reported by several observers. Ssobolew failed to find them in six cases of diabetes, and stated that in nine others they were abnormally few. Herzog found a

diminished number in three out of five cases. Weichselbaum and Stangl reached the conclusion that the number of islands may be diminished in diabetes, and, since the pancreas is almost always atrophic, the total number is still further curtailed. Opie, however, points out that the distribution of the islands varies in different parts of the gland, and that, while they may be almost absent in some parts, they may be numerous in others, and particularly in the tail of the organ. Before arriving at any conclusion as to the relative number of islands in any portion of the pancreas, it is, therefore, necessary to compare it with sections prepared from corresponding parts of the gland from normal individuals of the same age. This condition appears to have been fulfilled by Weichselbaum and Stangl, but they did not, however, separate cases in which the islands showed lesions from those in which they were apparently normal. Opie has compared the size and distribution of the cell islets in the head, body, and tail of the pancreas in eight cases of diabetes, and found that the figures obtained showed no constant departure from the normal. A striking diminution in the number of islets was seen in two cases, and in one of these, a child of fourteen in whom the diabetes was hereditary, he suggests that it might be due to a congenital defect of the gland. He concludes that "while diminution in the size of

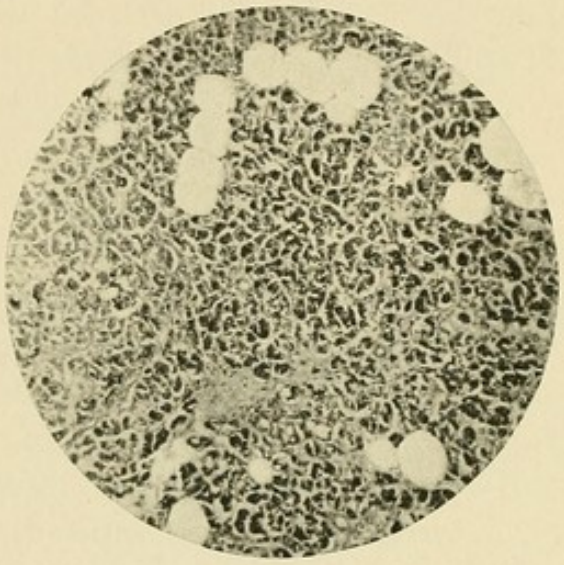

Fig. 112.—Chronic interstitial pancreatitis with fibrosis of the islands of Langerhans from a case of diabetes (× 40).

the gland, together with absolute and relative diminution in the number of interacinar islands, may occasionally explain the occurrence of diabetes, with our present knowledge it is unjustifiable to assume the existence of such functional deficiency when no lesion can be demonstrated by the methods at our disposal."

Most of the published cases of diabetes in which the condition of the islands of Langerhans is reported have been collected by Sauerbeck. He found that in one hundred and seventeen out of one hundred and fifty-seven there was some abnormality. If the purely quantitative changes are rejected, as being of too indefinitive a character, there remain ninety-eight (62 per cent.) in which qualitative changes were observed.

Most modern observers, who have systematically investigated the islands of Langerhans in diabetes, have either accepted the view that there is a causal relationship between the disease and lesions of the islands, or suspended judgment until further evidence is available. Hansemann, however, definitely states his conviction that no such relationship exists. He investigated thirty-four cases, and found that the islands were present in all. In some, where nearly the whole parenchyma had been destroyed by fat or interstitial fibrosis, he states that, although they were diminished in number, they were unchanged. In six cases he found the islands invaded by what he regards as hyaline connective tissue, but since they were not all affected and there was an accompanying interstitial fibrosis of the gland, it appeared to be a matter of chance whether the islands were involved or not, but he admits that he has not met with a case in which fibrosis affected the islands without diabetes being present.

Chauffard and Ravant met with swelling and increase of size in the islands of Langerhans, without glycosuria, in thirteen cases of enteric fever, two of pneumonia, and

one of erysipelas. They do not regard the condition as pathological, however, but consider it as a hypertrophic reaction. Salisbury Trevor observed similar changes in the cell islets in pneumonia and infective endocarditis.

Herxheimer, studying the cell islets in the cirrhotic pancreas so often found in diabetes, states that he found evidence of their new formation from the small ducts, but he regards the whole pancreas as controlling sugar metabolism, and thinks that diabetes is due to a functional lesion of the gland, which may or not be accompanied by visible morbid changes. In man he considers that the islets alone are inadequate for the prevention of diabetes, while in animals they appear to be sufficient. This statement is, however, not supported by any convincing evidence, and is in fact directly controverted, as regards human diabetes, by a case described by S. G. Scott, in which, although only the islands of Langerhans remained, no trace of sugar was found in the urine.

Even if the connection of the islands of Langerhans with diabetes is granted, a certain number of cases remain in which no lesion whatever of the pancreas has been discovered by competent observers. Opie met with four in his nineteen cases. Williamson eight in twenty-two, Ssobolew two in fifteen, and in twenty-three examined by Schmidt there was no change in eight, and in eight others the alterations were so slight as to be considered secondary to the diabetic condition. It may be contended that the specific diabetic disturbances of the pancreas are not necessarily connected with visible anatomical alterations of the islets, or in any other tissue of the gland, and, although it is possible that in some instances there may be minute alterations in the molecular arrangement of the cells which cannot be discovered with the microscope, we are at present unacquainted with any other method of demonstrating minute morbid changes, and

most perforce abide by the results obtainable by the means at our disposal. It is possible, however, that at the present time we include under the term diabetes several conditions, having somewhat similar symptoms, and all characterised by the presence of glycosuria, which are not due to the same cause. There is no doubt that those in which lesions of the pancreas are present form a larger class than is generally supposed, but it may prove that diseases of other organs or tissues are responsible for some, and that the cases in which the pancreas appears to be normal after death have a separate origin. At the same time it is well to bear in mind, as von Noorden has insisted, that scientific medicine has been so long under the influence of morbid anatomy that it is often difficult to realise that important disturbances of function may occur when microscopical examination reveals no distinctive pathological changes.

The association of arteriosclerosis, gout, syphilis, and alcoholism with diabetes is probably to be explained by the fibrotic and degenerative changes which each is capable of setting up in the pancreas. Cirrhosis of the liver is often found to coexist with chronic interstitial pancreatitis in diabetes, and both probably originate from the same causes. The apparently infective cases of diabetes may be due to the effects produced upon the pancreas by the entry of micro-organisms from the duodenum, and the history of digestive disturbances, which is not uncommon in diabetes, suggests that a chronic duodenal and gastric catarrh may in some instances give rise to the conditions favourable for the onset of a pancreatic lesion. Chronic pancreatitis has been repeatedly observed in association with acromegaly, and it appears probable the diabetes, transient glycosuria, and alimentary glycosuria that have been seen, not infrequently, to accompany this disease are to be referred to pathological changes in the pancreas.

We have seen that painting the pancreas with adrenalin, and a variety of other substances, gives rise to glycosuria, but that the action of the suprarenal extract appears to be of a specific and peculiar nature. Blum has produced temporary glycosuria by injecting suprarenal extract into the veins and subcutaneous tissues of animals, and the same result, but to a more marked degree, has been found by Herter and Richards to follow injections of adrenalin into the peritoneal cavity. These experiments suggest that there is some connection between the glycolytic action of the pancreas and the suprarenal bodies, and the anatomical picture presented by cases of so-called "diabéte bronzé" tends to favour this view.

Bronzed diabetes is closely related to the condition described by von Recklinghausen under the name of hæmochromatosis, in which the epithelial cells of the various glands of the body, and particularly of the pancreas and liver, show deposits of a reddish-yellow iron-containing pigment, the smooth muscle-fibres of the blood- and lymph-vessels, and of the walls of the gastro-intestinal tract, contain fine granules of a bright yellow, iron-free pigment, and there is hypertrophic cirrhosis of the liver, but, unlike simple hæmochromatosis, it is associated with a rapidly fatal form of diabetes mellitus. Although bronzing of the skin is present in the majority of cases, it is not constant. When present it is usually general and uniform, but is not accompanied by pigmentation of the mucous membranes, as in Addison's disease.

Hanot and Chauffard, who first described the condition in 1882, found, in one of their cases, of which they made a careful study, that there was advanced chronic interstitial pancreatitis, and other observers, who have had the opportunity of investigating the disease, have also found that the pancreas was affected. Where a microscopical examination of the gland has been made interstitial fibrosis has been found, the connective-tissue

spaces being much enlarged, and they, as well as the cells, have contained a deposit of reddish-yellow pigment. Margain has recently reported that, in a fatal case of bronzed diabetes he examined, some of the islands of Langerhans were preserved, but that their cells were crowded with pigment. Hanot and Chauffard believed that the diabetes was the primary factor in the disease, the changes in the liver and other tissues being due to diabetic alterations in the blood, and to the accompanying endarteritis, but Marie Acard, Dutourier and Jeanselme, and Anschültz think that the tissue changes result from a deposit of pigment in them, and that the pigment arises from a dissolution of hæmoglobin from some unknown cause. According to this view, the diabetes is a secondary phenomenon due to the changes in the pancreas. Opie, who has examined a case of hæmochromatosis, is of opinion that it is a distinct morbid entity, associated with chronic interstitial inflammation, notably of the liver and pancreas, and that, when the pancreatitis has reached a certain grade of intensity, diabetes mellitus ensues, and is usually the terminal event. He finds that the pancreatic inflammation is of the interacinar type, and that the islands of Langerhans are implicated in the lesion.

A few cases have been described in which there has been no glycosuria, although the whole of the pancreas has been apparently destroyed by malignant disease or inflammatory processes, but none are of recent date, and in most instances the proof of total destruction rests upon macroscopical examination alone. In view of the abundant experimental and clinical evidence now available, that the pancreas is essential for carbohydrate metabolism, the proof that its absence can be unattended by glycosuria must be exceptionally strong, although it must be admitted that a single well authenticated instance would call for a revision of the views at present generally held.

Minkowski, as we have seen, showed that if only part of the pancreas be removed in animals diabetes does not result, but the ability of the organism to perform its normal functions in carbohydrate metabolism is impaired, so that large doses of sugar give rise to temporary glycosuria. The capacity of the body to deal with carbohydrates is normally limited, and is not the same for all varieties of sugar. Glucose appears to have the highest limit (150 to 200 grams in one dose), lævulose can be taken in somewhat similar amounts without producing glycosuria (140 to 160 grams in a single dose), cane-sugar also can be taken in doses of 150 to 200 grams, but milk-sugar has a much lower limit (80 to 100 grams). According to v. Noorden, the assimilative capacity of normal individuals varies very considerably for maltose, for while there are some who can tolerate considerable quantities, there are others who possess a very low assimilation limit. According to him, this accounts for the appearance of sugar in the urine of some persons after even a moderate amount of beer has been taken. Pentoses are only assimilated with difficulty, and even the ingestion of so small a quantity as 30 to 50 grams is followed by the appearance of almost half in the urine. For starch no limit is known, for if as much as 400 or 500 grams are consumed in a few hours alimentary glycosuria does not occur.

Pathologically *alimentary glycosuria* occurs in certain nervous and brain troubles, in diseases of the liver, and as the result of lesions of the pancreas, as well as in some cases of acute febrile disease, and in acute and chronic alcoholic intoxication. The glycosuria met with in the two last groups has been attributed to disturbances of the liver, but v. Noorden considers that it arises from real, though transitory, disturbances of the pancreas, for the glycosuria is much more marked than is that met with in liver disease, the influence of glucose much ex-

ceeds that of lævulose, whereas in liver disease, as a rule, the organism reacts much more strongly to the latter, and glycosuria can be produced by an excess of starchy food.

The relation of the pancreas to alimentary glycosuria in man has been investigated by Willie, who gave 70 to 100 grams of grape-sugar to eight hundred patients, suffering from a variety of diseases, in the morning before food had been taken. The urine was examined before the test, and at intervals of two hours afterwards. Of the eight hundred individuals, seventy-seven subsequently died and were examined post-mortem. Alimentary glycosuria had been found in fifteen of these, and in ten there were present grave lesions of the pancreas, either primary, or secondary to growths in the stomach, liver, or gall-bladder.

Since pancreatic diabetes presents no characteristic clinical symptoms by which it can be recognised with certainty, its *treatment* differs in no essential respect from that by which it is sought to stay the progress of diabetes in general. Reliance must be placed mainly upon diet and the control of the hygienic condition of the patient. Although numerous drugs have been supposed to have a beneficial effect in cases where the pancreas was believed to be diseased, there is no evidence that a pancreatic lesion can be directly controlled by this means, except possibly, to a certain extent, by mercury in syphilitic cases. As it is probable, however, that some cases of pancreatic diabetes may arise from an infection reaching the gland by way of the intestine, drugs calculated to allay catarrh of the duodenal mucous membrane and control the intestinal flora may be of some service in preventing the progress of the disease. It is also possible that gastro-enterostomy and cholecystenterostomy, by draining the affected areas and putting them to rest, might in similar cases have a beneficial effect.

The satisfactory results following the administration of thyroid extract in myxœdema and sporadic cretinism have naturally suggested that the use of pancreatic extracts, or of the fresh gland, might be equally effectual in the treatment of pancreatic diabetes. In a few cases it has been claimed that some amelioration of the symptoms has been produced in this way, but the majority of observers are agreed that, although some improvement in the digestive powers may result, the glycosuria and other symptoms of the diabetic condition are uninfluenced. In order to avoid destruction of the ferments contained in the extract by digestion in the alimentary tract, subcutaneous injection has been resorted to, but with equally unsatisfactory results. Clinical experience, however, in these respects only confirms the experimental results obtained by Minkowski, Thiroloix, and others, who found that in depancreatised animals the administration of fresh pancreas or pancreatic extracts by the mouth, subcutaneously, into the peritoneum, or into the veins had no effect in controlling the glycosuria. It is possible that the action of the pancreas in carbohydrate metabolism may be a function of the living gland, and that, for this reason, extracts and preparations made from the dead organ may fail to be of use in diabetes, but the subcutaneous implantation of the pancreas of the lower animals into diabetics, contrary to what might be expected from experimental work on the grafting of pancreatic tissue beneath an animal's own skin previous to extirpating the gland, has not proved of any service as a therapeutic measure.

Basing their treatment on the effects of secretin as a stimulant of the pancreas, Moore, Edie, and Abram have employed an acid extract of duodenal mucous membrane in diabetes. They found that, when this was given by the mouth, the sugar in the urine gradually diminished in some cases, and finally disappeared in a few. In others, although

there was an improvement in the digestion, no effect on the sugar output was produced. Bainbridge and Beddard, however, have not noticed any amelioration of the symptoms in cases they have treated by this method, and suggest, as the result of their experience, that any improvement that takes place is to be attributed to the diet and not to the secretin. J. R. Charles has also failed to notice any good following the use of secretin in three cases of diabetes. The method is, as yet, in an experimental stage, and the number of cases in which it has been tried are too few to prove whether it is really efficacious in genuine cases of pancreatic diabetes or not. Even should it be shown eventually that acid duodenal extract can exert some influence in controlling glycosuria, it is open to question whether the treatment may not, in the end, do more harm than good, for the artificial stimulation of the diseased tissue that may remain in cases of pancreatic diabetes, although it may at first induce increased activity, is likely to eventually bring about fatigue, and cause more rapid degeneration than would have occurred if it had been let alone. The intravenous injection of secretin has been shown by Starling to give rise to acute inflammation of the intestines, and even to gastric ulcers, in animals, for the pancreatic juice is not met and neutralised by the acid gastric contents which normally cause the flow. This objection does not apply to the administration of secretin by the mouth, as the secretion will be gradual, and correspond to the acidity of the gastric juice reaching the intestine.

Cohnheim's work upon the effects of a mixture of pancreatic and muscle extracts in glycolysis has suggested the use of such a mixture in diabetes, and it has been employed for this purpose by Crofton.

The difficulty that attends all methods of treating diabetes is vastly increased by the obscurity of the etiology, but where it follows, or is associated with, evidences

of pancreatic or gall-stone trouble, the origin of the disease is plain, and, in the early stages, appropriate means of treatment can be adopted with a fair hope of success. We have already referred to four cases of cholelithiasis in our own experience that were accompanied by glycosuria, and in three of which operation was followed by disappearance of sugar from the urine. Gifford Nash's case of acute pancreatitis with glycosuria may also be cited as an example of the satisfactory results attending timely operative interference. It is essential, however, that the disease should not be too far advanced, and for this reason we strongly recommend that all cases of pancreatitis and gall-stones likely to give rise to a pancreatic lesion should be operated on with as little delay as possible after they have been diagnosed. As we shall show in a subsequent chapter, the early recognition of these conditions is not now a matter of great difficulty, if all the signs and symptoms to be obtained by a careful consideration of the clinical and pathological features of the case are taken into account, so that difficulty of diagnosis cannot be urged as a valid excuse for cases of pancreatitis being permitted to proceed untreated to a stage at which diabetes supervenes.

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CHAPTER XII

GENERAL SYMPTOMATOLOGY AND DIAGNOSIS

The varied and important part the pancreas takes in the digestive processes that go on in the intestine, and the equally important influence that it appears to exert upon the internal metabolism of the body, would naturally suggest that any departure from the normal would lead to such disturbances of function that the symptoms of diseases of the pancreas would be so marked as to make the diagnosis easy. But this is far from being the case for several reasons: First, it is seldom that the pancreas is diseased without other organs also being involved; for example, pancreatitis is very frequently associated with cholelithiasis; gastro-intestinal catarrh and catarrh of the bile and pancreatic ducts often coexist; ulcers or tumours of the stomach or duodenum may extend to, and involve, the pancreas; and affections of the liver, colon, or lymphatic glands may give rise to disease in the pancreas. Secondly, the digestive functions of the pancreas can be carried out, more or less completely, by other agencies, the stomach can deal with proteids, the salivary and intestinal glands have the power of digesting starches, and the bile and intestinal secretions can emulsify fat; moreover, the intestinal bacteria, as we have seen, possess the power of breaking down various food materials, and so interfering with the pathological alterations in the stools that might be expected in pancreatic diseases. Thirdly, a considerable portion of the gland may be necrosed and cast off, or otherwise disabled, and yet the remaining portion may apparently be sufficient to carry on the functions of the organ. Fourthly, in

some cases the pancreas may be the organ primarily at fault, and yet the most prominent symptoms may be caused by another organ that is involved secondarily; for instance, cancer of the head of the pancreas gives rise to intense jaundice and distension of the gall-bladder, suggesting to the uninitiated a primary affection of the liver or bile-ducts, but the symptoms are in reality due to gripping of the common bile-duct by the growth, and simple chronic pancreatitis may also cause jaundice for the same reason. Again, a tumour of the pancreas may compress the intestine and produce intestinal obstruction, or may press upon the neighbouring ganglia and cause most violent pain, mimicking that met with in spinal disease, aneurysm, etc. Thus it will be seen that in diseases of the pancreas very conflicting combinations of symptoms may arise, which may lead to great difficulty in diagnosis, unless some well-defined guiding principles can be established by which it may be determined, with a considerable degree of certainty, that the pancreas is, or is not, the organ primarily at fault. This we hope to show is not impossible.

The signs and symptoms which are present, to a greater or less extent, in most pathological conditions of the pancreas may be classified as follows: (1) physical signs, (2) digestive symptoms, (3) metabolic symptoms, (4) symptoms produced by artificial means.

1. Physical Signs.—(*a*) *Tumour.*—The situation of the pancreas, behind the stomach and in front of the spinal column, places it in a very unfavourable position for palpation, and, normally, if the patient be at all stout, it can only be felt indistinctly; but when the patient is thin, and especially in cases of gastroptosis, it can be readily defined, if the muscles are relaxed and a warm flat hand is applied firmly to the epigastric region. It is commonly stated in text-books that acute and chronic inflammation, and even abscess of the pancreas, rarely,

if ever, cause perceptible enlargement of the organ, but this is not correct, for in many cases a distinct swelling may be felt, which, in acute cases, is made up of the enlarged pancreas, with surrounding effusions of blood and inflammatory fluid and matted omentum; in subacute cases the swelling is due to suppuration; and in chronic inflammation it arises from tumefaction of the gland itself. In cancer of the head of the pancreas the only tumour that is ordinarily felt is that due to the enlarged gall-bladder, which can be readily palpated in a considerable proportion of cases. Tumours of the body or tail, as well as some growths of the head of the gland, can be readily distinguished, and by distending the stomach with gas, either by means of bicarbonate of soda and tartaric acid given in separate doses, or by pumping in air through the stomach-tube, the relation of the stomach to the tumour can be satisfactorily made out. Resonance on percussion, owing to the position of the stomach, unless this organ is empty, communicated non-expansile pulsation, and very slight movement on deep inspiration are characteristic of swellings of the pancreas. In cystic diseases of the gland a tumour is frequently, at first, the only symptom; the position and relation of such a tumour depend on the part of the organ from which it springs, as we shall show later. It will thus be seen that the absence of a tumour does not negative serious disease of the pancreas, but the presence of a swelling, when taken with other symptoms, affords valuable evidence in favour of a pancreatic lesion.

(*b*) *Fever.*—A rise of temperature is, as a rule, associated with acute and subacute pancreatitis, but only rarely with any of the more chronic forms of inflammation. Cystic disease, calculus, and new-growth do not generally give rise to fever. In acute pancreatitis the temperature may be high, but in some cases, as in the hæmorrhagic form, it is usually subnormal. The temperature in

suppurative pancreatitis is generally irregular, and may assume a hectic type, but occasionally it is subnormal. A persistent temperature of 101° F. to 102° or 103° F., associated with rigors, was observed by one of us in a case of pancreatitis with abscess formation. In cancer of the head of the pancreas the temperature is generally subnormal, although occasionally there may be fever from attendant complications, such as cholangitis and abscess of the liver. It will thus be seen that fever as a symptom of disease of the pancreas is extremely variable, and, alone, is no guide, though when associated with digestive, metabolic, and other signs, it may be of considerable assistance in making a differential diagnosis.

(*c*) *Pain and Tenderness.*—These symptoms, although important when present, are so variable that even their complete absence is no proof that the pancreas is normal. Both pain and tenderness are, as a rule, absent in malignant disease of the head of the pancreas, but in exceptional cases of carcinoma and sarcoma of the head, body, or tail the pain may be excruciating. This is due either to pressure on, or involvement of, the great sympathetic ganglia, or to pressure on, or invasion of, neighbouring viscera, particularly the stomach and duodenum. Small scirrhus tumours are, as a rule, characterised by absence of pain, while large growths are often marked by constant and extreme agony. In the various forms of pancreatitis pain and tenderness in the epigastrium are generally well marked. The more acute inflammations are characterised by excessive tenderness on pressure, the presence of a tender spot just above and to the right of the umbilicus, rigidity of the recti, and pain of an agonising character. The pain in hæmorrhage into the pancreas is intermittent, being at times severe and of a colicky character, then diminishing or disappearing, to return later with increased intensity. In chronic pancreatitis pain and tenderness, although usually present, may be but little marked. In

some cases, however, the pain is paroxysmal and severe, and epigastric tenderness is pronounced. Cysts are frequently painless and free from tenderness, but in some instances both pain and tenderness are well marked. Even in abscess of the pancreas pain is not a constant symptom. It may be absent, as in the case reported by Stibler, but in the majority of cases both pain and tenderness are pronounced. Calculus of the pancreas may exist for years undetected, and unsuspected, without causing any pain. If, however, the calculus reaches the orifice of the pancreatic duct, or is impacted in the ampulla of Vater, severe paroxysmal pain, resembling a gall-stone seizure, will occur and be associated with jaundice. As to the character of the pain, it may be continuous or paroxysmal, and may be limited to the epigastrium or radiate around either side of the thorax. Pain in the back, under the left scapula, or between the scapulæ, is more frequent than pain beneath the right scapula in pancreatic disease, thus serving to distinguish it from gall-bladder pain. "Cœliac neuralgia" was a term long ago applied to epigastric pain such as is associated with some forms of pancreatic disease, and such pain may radiate to the cardiac region and resemble angina pectoris, both in its intensity and in its effect upon the circulation. It will thus be seen that, while pain is a guide to diagnosis, it is not pathognomonic of any special form of pancreatic disturbance, except acute pancreatitis.

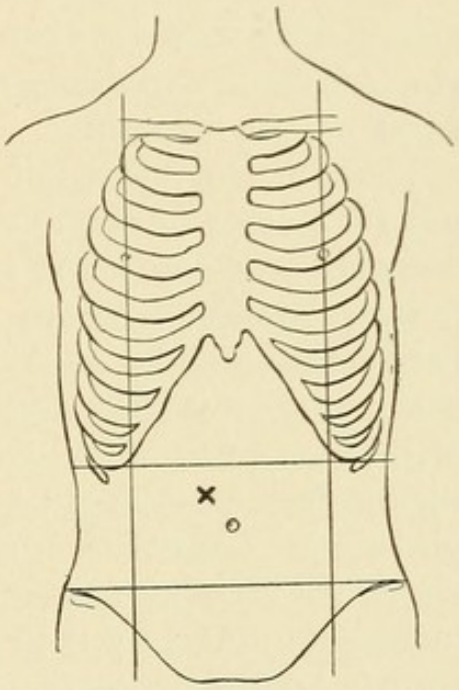

Fig. 113.—Most frequent site of the tender spot in inflammatory affections of the pancreas.

(*d*) *Pressure Symptoms.*—Owing to involvement of the portal vein, ascites is seen at times in the later stages of cancer of the pancreas, and, when there is also pressure on the inferior vena cava, œdema of the lower limbs will occur. Pressure on the portal vein may also cause enlargement of the spleen, and give rise to hæmorrhoids. In those rare cases where the duodenum is surrounded by, or partly surrounded by, the head of the pancreas, malignant disease, or even inflammation of the head of the gland, may lead to obstruction of the passage of the stomach contents, causing gastric dilatation and vomiting, as in pyloric stenosis.

The stomach, duodenum, and colon may also be pressed upon by cysts or new-growths of the pancreas, and be seriously displaced; the stomach, for instance, may be pushed upwards beneath the diaphragm or downwards below the umbilicus. Distension of the gall-bladder, with jaundice, is so frequently found in cancer of the head of the pancreas that it is now a well-recognised sign of the disease, but it must be remembered that in some cases of chronic pancreatitis a similar sequence of events may occur, the presence or absence of the sign in this instance being determined by the relation of the common duct to the head of the pancreas. In some cases the hepatic duct may be pressed upon when the common duct is free, as in a case coming under our observation, where, owing to a prolongation upwards of the pancreas being involved in a chronic inflammation of the gland, there was jaundice without distension of the gall-bladder. The pressure of a pancreatic cyst upwards, on to the under surface of the diaphragm, may cause dyspnœa, from interference with the functions of the heart or lungs, and, in cases of inflammatory effusion into the lesser peritoneal sac, there may be pressure on the pericardium, through the diaphragm, leading to distressing cardiac symptoms. Occasionally hydronephrosis may be produced by the pressure of pan-

creatic tumours on one or other ureter, and pressure on, or involvement of, the solar plexus may give rise to agonising pain.

(*e*) *Hæmorrhage.*—In inflammatory disease and malignant growths of the pancreas there is a well-marked hæmorrhagic tendency, which is not only seen at operation, but, in advanced cases, may be manifest by bleeding from mucous surfaces and by hæmorrhages into the skin or subcutaneous tissues, so that the patient bruises very readily. Profuse and uncontrollable hæmorrhage from the mucous surfaces was the cause of death in the case of pancreatitis above referred to, where there was a prolongation of the head of the pancreas upwards on to the hepatic duct, and in several cases of cancer of the pancreas operated on by one of us, bleeding has cost the patient his life. For instance, this occurred in a case sent by Professor Clifford Albutt, which was operated on in 1888. Cholecystotomy was followed by persistent oozing of the blood from the interior of the gall-bladder, and from the stitch punctures, which resisted all the then known remedial measures, and proved fatal on the ninth day. In another case of cancer of the head of the pancreas, sent by Dr. W. Scatterty, of Keighley, a cerebral, hæmorrhage on the tenth day produced a fatal result. In neither of the cases was there any peritonitis, or other cause than the hæmorrhage, to account for death. That the hæmorrhage in these cases is not entirely dependent upon the jaundice, but is associated with the changes induced in the blood by the pancreatic lesion, is shown by the fact that patients with equally profound jaundice, but in whom there is no disease of the pancreas, do not bleed to anything like the same extent. Thus, in a patient seen with Dr. T. Churton in 1889, the jaundice was quite as deep as in either of those just quoted, but there was no hæmorrhage, although the man lived several weeks, and ultimately died from suppurative cholangitis and exhaus-

tion, for the obstruction was dependent on cancer of the common bile-duct above the entrance of the pancreatic duct. The tendency to hæmorrhage, both at operation and after, can be successfully counteracted by the administration of calcium chloride, in 30-grain doses, thrice daily, for from twenty-four to forty-eight hours before operation, and by enema, in 30-grain doses, twice daily for forty-eight hours afterwards. The following cases illustrate the efficiency of this procedure subsequent to operation, and the danger that may arise from its absence or too early disuse:

A woman, aged thirty-eight years, was suffering from deep jaundice, associated with gall-stones in the common duct and chronic pancreatitis. There was no bleeding at the time of the performance of duodeno-choledochotomy, as calcium chloride had been administered for several days before operation. The drug was inadvertently omitted after operation, and on the third day violent hæmorrhage occurred, which was arrested by opening up the wound and packing with gauze, and at the same time giving calcium chloride in 60-grain doses twice, and afterwards in 30-grain doses for several days. No recurrence of bleeding occurred and a good recovery was made.

In the case of a male patient, aged forty-two years, suffering from cirrhosis of the liver, gall-stones in the common duct, and chronic pancreatitis, no bleeding occurred at operation, owing to the previous administration of lime salts. In consequence of the absence of hæmorrhage the calcium chloride was left off the second day after operation. Bleeding occurred very freely on the sixth day, in the form of general oozing, which was permanently arrested by the free administration of calcium chloride, after which recovery occurred.

In a case of suppurative catarrh of the pancreas in a gentleman, aged sixty-five years, the same freedom from hæmorrhage was found at operation, after the administration, for some days, of calcium chloride, which was not continued, as the rectum was intolerant of injections. On the seventh day free bleeding occurred, which was

arrested by giving thirty grains of calcium chloride every two hours by the mouth.

(*f*) *Jaundice.*—The now well-recognised relation between gall-stone trouble and pancreatic disease would lead one to expect that jaundice would be a frequent accompaniment of diseases of the pancreas, but the symptom is by no means constant. The relation of the common bile-duct to the duct of Wirsung, and to the head of the pancreas, is generally the determining factor. If, as is the case in 38 per cent. of bodies (Helly), the common duct passes behind the head of the pancreas, either an acute or a chronic pancreatitis, or even a cancer of the pancreas, may run its course without the appearance of jaundice; but if the common duct lies in a deep groove, or is embedded in the head of the gland, as occurs in 62 per cent. of cases, either pancreatitis or growth of the head of the organ must necessarily compress the bile-duct and lead to jaundice of greater or less intensity. It may perhaps be only a coincidence, but it is noteworthy that in 62 per cent. of our cases of chronic pancreatitis associated with cholelithiasis bile-pigments were found in the urine before operation, and in 38 per cent. there was neither jaundice nor bile-pigment in the urine. Chronic pancreatitis, not associated with the presence of gall-stones in the common duct, was accompanied by jaundice in 16 per cent. of our cases, the icterus in these instances being probably due either to compression of the common duct by the swollen head of the pancreas, or to an ascending catarrh from the duodenum, which simultaneously involved the pancreatic and biliary passages. In pancreatic calculus jaundice may occur if the stone lodges in the ampulla of Vater. Acute hæmorrhagic pancreatitis may be accompanied by slight jaundice, especially when it results from the impaction of a small gall-stone in the duodenal outlet of the ampulla of Vater.

Deep jaundice, with a distended gall-bladder, is significant of cancer of the head of the pancreas, whereas if the cause of the jaundice be gall-stones in the common duct the gall-bladder is nearly always contracted and cannot be felt. The jaundice met with in cancer develops without pain, slowly and insidiously, but steadily. As the cachexia increases the patient's skin assumes a ghastly slaty appearance in many instances, so that instead of the saffron yellow colour of cholelithiasis there is seen the so-called "black jaundice."

(*g*) *Emaciation.*—Ever since pancreatic disease has been recognised, emaciation has been regarded as a striking symptom. In some cases of chronic inflammation there is a very marked loss of flesh, which is rapidly regained after a cure of the condition has been effected by operation. Thus, a patient who was operated on by one of us for the removal of a calculus obstructing the pancreatic duct had lost eight stones in a little over two years, but rapidly regained his normal weight after the operation. In another, and similar case, the patient had lost five stones in three months, but gained three stones in the same period after his condition had been relieved by operation. It is not surprising that emaciation should occur in cancer of the pancreas, in which, indeed, it is most marked, or in diabetes of pancreatic origin, but it may also be met with in cystic disease, as in Kuster's case, in which the patient lost two stones five pounds in four months, and it is also seen in calculus disease. The disturbance of digestion may afford a sufficient explanation in some cases, but in malignant disease and cases of atrophy of the gland, interference with the metabolic functions of the pancreas are probably, in part, responsible for the rapid wasting that is met with in these conditions.

2. Digestive Symptoms.—(*a*) *Dyspepsia and Alteration of Appetite.*—Dyspeptic disturbances are very constantly

associated with affections of the pancreas. They take the form of anorexia, pain, and fulness after food, flatulence with offensive eructations, heart-burn, nausea, distaste for fats and for meat. In the case of a woman aged twenty-eight, to be referred to later under "Chronic Pancreatitis," where a biliary fistula was established in order to relieve the jaundice and by drainage to cure the pancreatitis that was causing pressure on the common bile-duct, all the above symptoms were well marked, both before the operation and when the fistula was discharging, and the patient had such a loathing for food that she became greatly emaciated. Within twelve hours of a cholecystenterostomy being performed, by which the pancreatic juice and bile were diverted into the duodenum, she expressed herself as hungry, a sensation she said she had not felt for many months. During the month succeeding the operation she put on flesh rapidly, and three months later had gained two stones in weight. In several cases where dyspeptic symptoms have been pronounced, both in simple and malignant disease of the pancreas, the administration of pancreatic preparations after meals has been found to give marked relief, and the patients have gained in weight.

(*b*) *Nausea and Vomiting.*—These symptoms are frequently associated with acute pancreatitis, and, in some instances, the vomiting may be so violent as to suggest intestinal obstruction. In other forms of pancreatic disease vomiting is not a common symptom, and, when present, is often due to neighbouring organs—stomach or duodenum—participating in the trouble or being pressed upon. There is nothing specially characteristic in the vomited matter, unless, as rarely occurs, extremely offensive pus and altered blood are brought up, as in cases where a pancreatic abscess has ruptured into the stomach. In one of our cases of erosion of the pancreas by chronic gastric ulcer the pus vomited was so offen-

sive that the nurses in attendance were made sick by the odour. The case was treated successfully by gastro-jejunostomy. In acute pancreatitis altered blood, the so-called "black vomit," is seen at an earlier stage than in any other peritoneal condition.

(*c*) *Fæces.*—The condition of the fæces furnishes, in many instances, what might almost be termed a characteristic sign of pancreatic disease. In these cases the motions are exceedingly bulky, soft, greasy, and pale. They contain undigested fat and muscle fibre, and are extremely offensive. Patients frequently state that they suffer from diarrhœa, but investigation will show that this is hardly correct, for, although the stools are bulky and soft, they are not liquid in consistency. The symptom is a very noticeable one, and, when it occurs in cases of jaundice, may nearly always be taken as indicating that the pancreatic functions are being interfered with, either by an interstitial pancreatitis or some other form of pancreatic disease. It is more common in inflammatory conditions than in cancer, probably because the appetite is more interfered with by the latter than the former, so that in pancreatitis the full effects of the lack of digestive powers are seen. For the same reason the symptom is more apt to be noticed in the earlier than in the later stages of pancreatic affections, unless large amounts of milk are being given, when the bulk of it may pass away in the form of spurious diarrhœa. In some cases there is constipation, the motions being still very bulky, however, and, as a rule, pale.

The bulk of these motions, out of all proportion to the amount of food taken, is to be attributed partly to the abnormal quantity of undigested food materials that they contain, and partly to the excessive fermentation that takes place in the intestines. Their frequency is due to their bulk, but is no doubt contributed to by the excess of irritating by-products they contain. The ques-

tion of their lack of colour has already been discussed (page 225), but it may be repeated that it does not necessarily arise from the absence of bile, as precisely similar stools may be seen in cases of pancreatic disease when there is obstruction of the biliary passages, and when there is no obstruction whatever to the free flow of bile into the intestine.

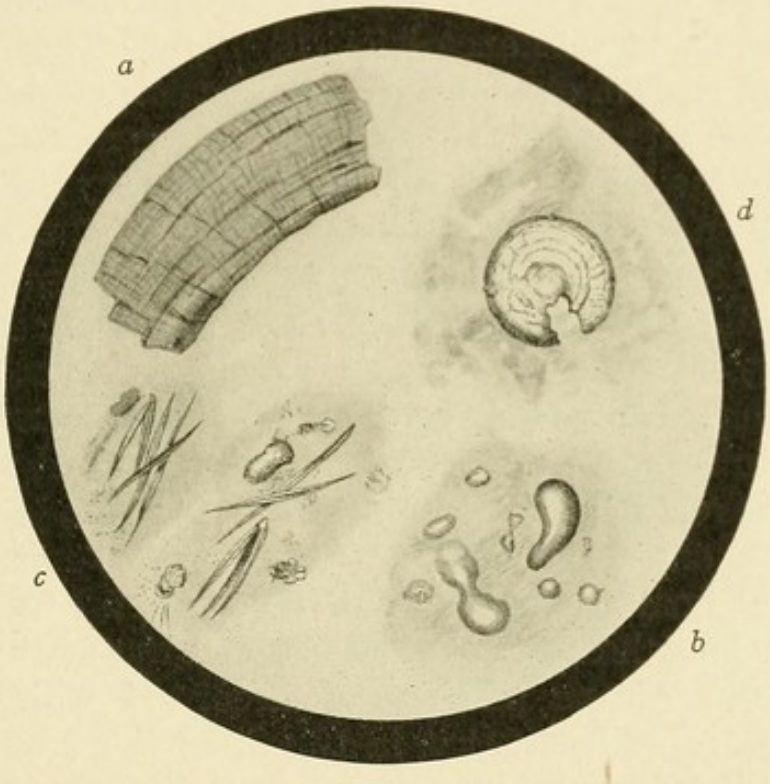

Fig. 114.—Microscopical characters of the residues met with in the stools in case of pancreatic disease and biliary obstruction: *a*, Striated muscle fibres; *b*, fat globules; *c*, free fatty acid crystals; *d*, combined fatty acid (soap) crystals.

Steatorrhœa or fatty stools have long been recognised as a symptom of disease of the pancreas. Kuntzmann, in 1820, described the case of a man who died from chronic induration of the pancreas, with complete obliteration of the common bile-duct and pancreatic duct, where large stools containing undigested fat were seen. In his record of seven cases of disease of the pancreas, Bright, in 1833, noted an excess of fat in the fæces of three. Fles, in 1864,

reported the case of a diabetic, who had eaten much bacon and fat meat, with stools containing such a quantity of fat that it could be skimmed off the surface by the ounce. The fat disappeared when an emulsion of calf pancreas was administered, but reappeared as soon as the emulsion was omitted. The patient died of phthisis, and post-mortem the pancreas was found to be replaced by fibrous tissue, with scarcely any recognisable trace of gland substance left. In many of the earlier recorded cases of steatorrhœa the pancreatic disease was associated with jaundice, and there was some doubt as to the part the lack of bile played in producing the condition. More recent observations have shown, however, that fatty stools occur in diseases of the pancreas independently of jaundice, and that in such cases the steatorrhœa is to be attributed directly to the pancreatic lesion. Fitz, of Boston, in an address before the Congress of American Physicians and Surgeons in May, 1903, gave in tabular form the relationship between visible fæcal fat, jaundice, diabetes, and pancreatic disease in twenty-nine cases collected from the literature of the subject. He found that in about three-fifths the steatorrhœa was attributable to disease of the pancreas unassociated with either jaundice or diabetes, that in two-fifths there was pancreatic disease with either jaundice or diabetes in about equal proportions, and that in a few instances there was a combination of pancreatic disease, diabetes, and jaundice.

In the following case, reported by Oser, the appearance of steatorrhœa in pancreatic disease, before the onset of jaundice, is well shown:

A woman, aged thirty-nine years, had had diarrhœa since the summer of 1892. The patient became emaciated, yet the appetite remained good. Fæcal evacuations appeared regularly every night, were unusually copious, of the consistency of thick porridge, and of cadaverous

odour, chocolate-coloured, and always abundantly covered with fat rings. On January 11, 1893, he saw the patient for the first time and found steatorrhœa. The investigations of the stools gave the following results: "Large in amount and of the consistency of thick porridge; in the sediment were scattered white particles. Microscopic examination showed: (1) very numerous fragments of striated muscle in the main with well-preserved structure; (2) numerous fat acid needles and fat drops; and (3) bacteria and detritus. After drying the stools for several days on the water-bath in order to determine the amount of fat, there were obtained 4.6325 grams of solid substance, in which 2.1265 grams were fat, representing 45.8 per cent. of the dried residue. The other extract consisted almost entirely of neutral fat." On January 18th he found in the epigastrium a distinct, hard, round tumour, which was diagnosed as carcinoma of the head of the pancreas. In March jaundice developed. At the beginning of April an exploratory laparotomy was undertaken and the diagnosis confirmed.

Fatty stools have been most frequently described in connection with cancer of the pancreas, but they have also been met with in fibro-adenoma (Biondi), calculi (Gould, Chari, Reeves, Cowley, Capparelli, etc.), cysts (Gould, Goodman, Bull, etc.), syphilitic atrophy (Demme), fibrosis (Kuntzmann), fatty degeneration (Reeves, Motta), abscess (Harley), and diabetes (Silver, Le Nobel, Hirschfeld, etc.). In most instances reliance has been placed upon naked-eye observations, and in only a few have actual determinations of the amount of fat present been made. Ziehl states that, in a case of cancer of the pancreas with jaundice that he investigated, the fat formed about 50 per cent. of the dry weight of the fæces, and Demme found from 64 to 73 per cent. of fat in the asbestos-like fæces of a case of congenital syphilis, with atrophy of the pancreas, that he examined.

In some cases, where fat is parted with in abundance, the greasy bulky motions, occasionally coated with oil which

may float on the surface of the urine passed at the same time, are sufficiently striking to attact the attention of the patient himself, but in others, although a large amount of fat may be passed, it can only be recognised on chemical examination, as our own experience has frequently demonstrated. It is therefore essential, if full advantage is to be taken of the occurrence of steatorrhœa as a symptom of disease of the pancreas, that the stools should be submitted to careful quantitative analysis. The method we have described in a previous chapter gives satisfactory results for clinical purposes, and has the advantage of occupying much less time than the processes usually adopted; further, it has the additional advantage of giving not only the amount of unabsorbed fat present in the stools, but of supplying information as to quantities of saponified and unsaponified fat that the motion contains, with but little extra trouble.

We have now employed this method of investigation in a large number of cases, and found that in many it has given results of the greatest value in diagnosis. As a rule, it has been found that when the functions of the pancreas have been seriously interfered with there has not only been an excess of "total fat," but that the relation between the "neutral fats" and combined "fatty acids" has been disturbed, the former being in excess, whereas in cases of simple jaundice or biliary obstruction, although the amount of "neutral fat" may also have been abnormal, the combined "fatty acids" formed the larger proportion of the fat in the dry fæces. In some cases of malignant disease of the pancreas as much as 93 per cent. of the dry weight of the fæces has been found to be fat, and even in chronic pancreatitis we have found from 80 to 82 per cent. The average amount in malignant disease, however, has been 77 per cent. In chronic pancreatitis more than 60 per cent. has been uncommon, and in some instances an amount within the limits for a normal mixed

diet has been met with. The "neutral fats" in cancer of the pancreas have ranged from 69 per cent. to 31 per cent., and the combined "fatty acids" from 36 per cent. to 3 per cent., with an average for the former of 50 per cent., and for the latter of 27 per cent. The "neutral fats" and combined "fatty acids" are normally present in equal proportions, but in chronic pancreatitis an average of 32 per cent. of the one and 18 per cent. of the other has been obtained. In our cases of biliary obstruction not associated with pancreatitis, on the other hand, the average amount of "neutral fat" has been 18 per cent., and of combined "fatty acid" 23 per cent., the "total fat" being 42 per cent.

In some cases of undoubted pancreatic disease, however, we have found that there was no excess of fat in the stools, and that even where an excess was present the relation between the "neutral fats" and combined "fatty acids" was not markedly disturbed, or else that there was a more or less marked excess of combined "fatty acid," contrary to what might have been expected. These variations have usually been met with in cases of pancreatitis, and generally in the earlier stages of the disease. The absence of an excess of fat in these cases is to be explained (1) by the food containing an abnormally small proportion of fatty material owing to the distaste of the patient for fat; (2) by the fat being of a readily digested and easily absorbed kind (*e. g.*, milk, etc.); and (3) by the action of the fat-splitting ferment of the stomach. The relatively high proportion of combined "fatty acids" may be accounted for (1) by the action of fat-splitting bacteria in the intestines; (2) by the examination being made at a comparatively early stage in the disease, when the flow of pancreatic juice is not diminished, or may be actually increased; and (3) by an associated enteritis hurrying the contents of the intestine onwards to the large bowel before they have had time to be completely absorbed.

Microscopical examination of the fæces may sometimes be of assistance when a chemical examination, for various reasons, is impracticable. In serious pancreatic disease the stools show numerous fat globules and many free fatty acid crystals. The latter, together with crystals of combined fatty acids, are also seen in jaundice, but no fat globules are usually met with in this condition, unless it is combined with disease of the pancreas. Microscopical examination, however, is only of use, as a rule, in confirming an opinion based upon the naked-eye characters, and is far inferior as a diagnostic aid to a chemical investigation.

In interpreting the results of an examination of the fæces for undigested fat it has to be borne in mind that, in addition to diseases of the pancreas and jaundice, an excess of fat may arise from (1) an abnormal quantity being taken in the food, for the capacity for digesting and absorbing fat is limited and probably varies somewhat for different individuals; (2) from diseases of the intestines and mesenteric glands that interfere with absorption, such as sprue, tuberculosis, etc.

If these conditions can be excluded steatorrhoea is suggestive of disease of the pancreas, especially if jaundice is absent, and even if there is obstruction of the biliary passage an excess of "neutral" fat over combined "fatty acid" points to there being some interference with the fat-splitting functions of the pancreas in the majority of cases. Disappearance of the excess of fat in the stools on the administration of preparations of pancreas after meals tends to confirm a diagnosis of pancreatic mischief.

The presence of *azotorrhœa* as a valuable symptom in diseases of the pancreas was first recognised by Fles in 1864. He found in the stools of a diabetic, who was proved post-mortem to be suffering from chronic interstitial pancreatitis, large numbers of undigested muscle fibres, which disappeared when calf's pancreas was administered

daily, and reappeared when it was omitted. Le Nobel subsequently reported a similar case. Harley found muscle fibres in the fæces, in large quantities, in a case of pancreatic abscess, Kuster in a case of pancreatic cyst, Lichtheim in a patient with pancreatic calculi, and v. Ackeron and Oser have described cases of cancer of the pancreas in which the stools contained an excess of striated muscle fibres. In twenty out of twenty-four of our cases of cancer of the pancreas, included in the table on page 214, numerous muscle fibres were found microscopically, but they were only present in sixteen out of fifty-six cases of chronic pancreatitis. An abnormally large number was also observed in one out of eight cases in which there was jaundice but no disease of the pancreas, and in two out of twelve cases in which there was a stone in the gall-bladder or common duct but no pancreatic disease. It will thus be seen that while an excess of undigested muscle fibres is frequently met with in malignant disease, it is not such a common symptom in pancreatitis. It is usually only seen in advanced cases of cirrhosis, or in other lesions where a great part of the secreting tissue has been destroyed, and the formation of pancreatic juice is very seriously interfered with.

Azotorrhœa is not so readily noticed as steatorrhœa, and attention is hardly ever drawn to it by the patient. In some instances the undigested muscle can be recognised by the naked eye, but, in most, a microscopical examination is necessary. Microscopical examination is, however, likely to prove misleading unless a considerable number of preparations are examined and muscle fibres are found in all; moreover, it must be remembered that if much meat enters into the diet, or there is an enteritis by which the food material is hurried through the intestine, an excess of muscle fibres may be met with when there is no disease of the pancreas. It must also be borne in mind that gastric digestion is necessary as a prepara-

tion for the work of the pancreatic juice on meat, for if the connective tissue binding the muscle bundles together has not been attacked by the gastric juice, the pancreatic secretion can only act from the surface, eating its way slowly inwards, and consequently undigested muscle fibre will be passed in the stools.

As the result of his observations on the different behaviour of tissue elements to the gastric and pancreatic juices, Schmidt found that the nuclei of cells were digested by the pancreatic but not by the gastric secretion. He therefore concluded that if undigested tissue nuclei reappear in the fæces they afford evidence that the functions of the pancreas are being unsatisfactorily performed, and he suggested that, under appropriate conditions, this might serve as a test of pancreatic efficiency. Schmidt advises that small cubes of fresh, "marbled" beef, about 0.5 to 0.75 cm. thick, should be hardened in alcohol, placed in little silk-gauze bags, and preserved in alcohol until required. Before use they are to be well washed in water for several hours, placed in a wafer, and given with the food at noon for several days. The bags can be easily recovered from the fæces, on rubbing them up in water, and, after they have been washed, the contents can be examined fresh, after treatment with acetic acid or methylene-blue, or they can be hardened, cut, and stained. He states that the nuclei are never preserved in disorders of the liver, intestine, or stomach, but that they are found intact in destructive lesions of the pancreas, and in animals after the pancreas has been removed.

The disadvantages of the method appear to be that the demonstration of the nuclei is not always easy, single nuclei remain unchanged in intense diarrhœa, even when there is no disease of the pancreas, and the nuclei may disappear as the result of putrefactive changes in the intestine, particularly if the material is retained in the bowel more than thirty hours. Schmidt therefore insists that all,

or at least most, of the nuclei should be preserved unchanged before it is inferred that the pancreas is diseased. Partial extirpation of the pancreas was found not to produce diagnostic changes, and it is therefore improbable that the method is of great value in any but the most advanced and serious pancreatic lesions.

The fæces are normally neutral or faintly alkaline to litmus, but in many cases of pancreatic disease we have found that they were distinctly acid. This alteration of reaction, although by no means constant or pathognomonic of pancreatic lesions, may sometimes serve as a confirmatory sign. The specimen should be examined as fresh as possible, and the sample to be tested should be taken from the centre of the fæcal mass, not from the surface. It can be applied to moistened litmus paper on a glass slide, which is then examined on the reverse side, or a fragment may be added to a little neutral litmus contained in a test-tube, which is centrifugalised, after it has been well shaken.

One of the most serious difficulties arising in connection with the diagnosis of diseases of the pancreas is the differentiation of the jaundice due to cancer of the head of the gland from that occurring in chronic pancreatitis and common-duct cholelithiasis. A chemical examination of the fæces for *stercobilin* may, in many instances, afford very considerable assistance and supply valuable confirmatory evidence. The method of investigation we have employed has been described on page 213. Obstruction of the common duct in most cases of cancer of the head of the pancreas, at the time they usually come under observation, is, we have found, generally complete, or almost complete, and the fæces are therefore free from stercobilin or contain but faint traces. In common-duct cholelithiasis and chronic pancreatitis, on the other hand, it has been our experience that the obstruction is rarely absolute, so that the fæces give a

distinct, although often subnormal, reaction for stercobilin. In the table on page 214 it will be seen that twenty-two out of twenty-four cases of malignant disease of the pancreas gave no stercobilin reaction, in two traces were found, and in one only was there a well-marked reaction. In eighteen cases of chronic pancreatitis, with jaundice and obstruction of the common duct, there was a well-marked reaction for stercobilin in all but six, and in these six traces were found. Stercobilin was also present in the fæces of eight cases of common-duct cholelithiasis with jaundice but no affection of the pancreas, in considerable amounts in five, and in small quantities in three.

Blood may be noticed in the motions occasionally, but it is not a regular symptom until the hæmorrhagic tendency occurs later in the disease, or unless there happens to be a malignant growth ulcerating into the intestine. Abscesses of the pancreas and pancreatic cysts have been known to rupture into the bowel and their characteristic contents have been found in the motions, or even in the vomited matter, as occurred in one of our cases. A necrotic pancreas has been passed through the intestine, and cases have been reported by Leichtenstern and Minnich in which pancreatic calculi have been passed per anum.

(*d*) *Sialorrhœa Pancreatica.*—An increased flow of saliva has been noted by some observers in disease of the pancreas, and particularly in cases of pancreatic calculi (Holzmann, Capparelli, and Guidiceandra) and cysts of the pancreas (Battersby and Ludolph). It has been supposed to be due to a reflex excitation of the salivary glands. The occasional association of pancreatitis with parotitis suggests that there is some obscure connection between the buccal and abdominal "salivary glands," but excessive salivation is such a very rare occurrence in pancreatic disease that it is possibly accidental and

cannot be relied upon as an aid to diagnosis. We have observed it in two at least of the cases that have come under our notice, and have recently met with a third in which it was one of the symptoms that most seriously troubled the patient. In this instance the salivation ceased in a most striking manner within forty-eight hours after he had been operated on for chronic pancreatitis.

3. Metabolic Symptoms.—(*a*) *Diabetes and Glycosuria.*—Glycosuria is by no means a common symptom of pancreatic disease, and cannot be relied upon as a diagnostic symptom. When present it indicates a serious, although not necessarily hopeless, condition. The relation of diabetes to disease of the pancreas has been discussed in the chapter on diabetes, and it will be recollected that both experimental and clinical observations have shown that glycosuria occurs only when the greater part of the pancreas has been removed or destroyed. The appearance of sugar in the urine, along with other signs of disease of the pancreas, therefore points to a wide-spread and advanced lesion. This is particularly the case in chronic interstitial pancreatitis of the interlobular type, which is the form that follows obstruction of the ducts by calculi, and is produced by ascending catarrhal inflammations from the duodenum. Interacinar pancreatitis gives rise to glycosuria at an earlier stage, but appears to be a much less common disease than the interlobular variety. Malignant disease of the pancreas rarely gives rise to diabetes, and then only, as a rule, when the whole organ has been destroyed by the growth.

(*b*) *Maltosuria and Pentosuria.*—The sugar met with in diseases of the pancreas is usually dextrose, but occasionally maltose has been found, and very rarely there would appear to be pentosuria. Neither maltosuria nor pentosuria can be regarded as pathognomonic of pancreatic diseases, and they are of such rare occurrence as to be of no practical importance.

(*c*) *The "Pancreatic" (Cammidge's) Reaction in the Urine.*—The original method of performing this reaction, as described by one of us in 1904 (see page 245), has to a large extent been superceded by the improved method (page 252). The former, in our hands, had proved exceedingly useful in many anxious and doubtful cases, but, as the interpretation of the results it yielded were largely dependent upon the experience of the observer, it was difficult for those who had not the opportunity of frequently performing the test to satisfactorily apply it in practice. The improved method has, we hope, overcome this difficulty, and also removed some of the possible sources of manipulative error in inexperienced hands.

We have regularly employed the improved reaction since the early part of 1905, and, as the table on page 255 shows, have found that a positive reaction may be expected in all cases where there are active inflammatory changes in the pancreas. Acute pancreatitis can thus be distinguished from intestinal obstruction, and other conditions with which it is liable to be confused, and chronic pancreatitis, associated with obstruction of the common duct by gall-stones, or secondary to duodenal catarrh, can be differentiated from simple cholelithiasis and jaundice, etc., for which a distinct method of treatment may be required. It is always advisable to control the urine examination by an investigation of the fæces, for if the results agree the chances of a mistaken opinion are considerably reduced, and are probably very small, if the analyses have been conducted by a competent observer. A chemical examination of the fæces is particularly useful in suspected cases of malignant disease of the pancreas, for, although no reaction is obtained by the improved method in about 75 per cent. of such cases, a crystalline deposit, indicating an associated inflammatory lesion, is met with in the remaining 25 per cent.

Clinically it is often a matter of extreme difficulty to

differentiate chronic inflammation of the pancreas from cancer, but if the results of a complete examination of the urine and fæces, carefully and conscientiously performed, are considered in conjunction with the history and symptoms, the chance of an erroneous diagnosis is materially reduced, even in those cases where the spread of the growth is giving rise to secondary inflammatory changes in the adjacent gland tissue. In our experience a characteristic "pancreatic" reaction in the urine has always been associated with evidence of disease of the pancreas at operation, or post-mortem, in all cases where it has been possible to investigate the condition of the gland, and information kindly supplied to one of us by others regarding cases examined for them confirms our opinion of the clinical value of the test. Confirmatory evidence is also afforded by the way in which the reaction disappears in patients who have suffered from pancreatitis, after steps have been taken to deal with the condition by operative means, and the uniform manner in which gall-stones in a common duct passing through the head of the pancreas have been associated with a positive reaction in the urine, whereas when the duct has passed behind the pancreas the presence of calculi has not given rise to any reaction. A striking demonstration of the diagnostic value of the test was afforded by a case already referred to in the chapter on diabetes. The urine from this patient, who suffered from a duodenal growth, gave no reaction when first examined, but later gave a well-marked result, which was shown at operation to be due to an invasion of the pancreas by the growth.

(*d*) *Test for Fat-splitting Ferment in the Urine* (*Opie*).—This test has only been employed by Opie in one case of acute hæmorrhagic pancreatitis, and there he obtained evidence that the urine contained a fat-splitting ferment. We have had no experience with it in acute pancreatitis, and are not acquainted with any published accounts of

cases in which it has been tried. If future experience should confirm Opie's observation, and show that fat-splitting ferments are constantly present in acute pancreatitis, a most useful addition will have been made to our means of diagnosing the condition.

(*e*) *Indicanuria.*—An increased excretion of indican and ethereal sulphates in the urine has been considered, by some writers, as an indication of disease of the pancreas. There are others, however, who have advanced reasons why the excretion of these substances should be diminished. There is no doubt that in many cases an abnormal amount of indican is found in the urine, but in our experience there is just as frequently no excess, and it is probable that the condition of the urine with regard to this substance is dependent upon factors of which the condition of the pancreatic secretion is only one, and that not the most important. Indicanuria is not, therefore, of any great value in the diagnosis of diseases of the pancreas, and the same may be said of an increase in the proportion of ethereal sulphates.

(*f*) *Reduction in the Excretion of Phosphates.*—A reduced amount of phosphates in the urine when on a milk diet, owing to non-splitting of the nuclein constituent of the caseinogen, has been noted in cases of pancreatic disease associated with a diminution or absence of the secretion. In order that this test may be applied it is necessary that the patient should be placed upon a milk diet for several days, and that a regular estimation of the phosphates in the total excretion of each twenty-four hours should be made. Since the excretion of phosphates is also diminished in pneumonia and other acute febrile diseases, in chronic and acute nephritis, and in gout and during pregnancy, these must first be excluded, and it is advisable that the diminution should be shown to be dependent upon failure of the pancreatic secretion by watching the

effects produced by the administration of preparations of pancreas with the food.

(*g*) *Oxaluria.*—A well-marked deposit of calcium oxalate crystals has been found in 63 per cent. of our cases of chronic pancreatitis, and, although we do not lay much stress upon it as an aid to diagnosis, such a deposit may be regarded as tending to confirm evidence obtained by other means.

(*h*) *Lipuria.*—The presence of fat globules in the urine has been noted in a few cases of pancreatic disease. It is such a rare occurrence, however, and may be due to so many different causes, that it is to be regarded rather as a curiosity than as a diagnostic sign of any practical value.

(*i*) *Fat Necrosis.*—The recognition of fat necrosis by the surgeon who opens the abdomen to relieve symptoms associated with peritonitis in its upper part, is of the utmost importance, as, in practically all cases, it may be taken to indicate a grave lesion of the pancreas, probably hæmorrhagic, gangrenous, or suppurative inflammation. It is said not to occur generally with suppurative inflammation, but in a case, to be referred to subsequently, most extensive fat necrosis was found with a subdiaphragmatic abscess of pancreatic origin. It has also been said that the presence of extensive fat necrosis is a fatal sign, but this is not invariably so, for Truhart has collected ten cases in which the diagnosis was made, and yet an immediately fatal issue did not follow, and we have had the opportunity of observing one case in which complete recovery took place after operation in a patient with acute pancreatitis in whom fat necrosis was well-marked and diffuse.

4. Special Symptoms Obtained by Artificial Means.—(*a*) *Alimentary Glycosuria.*—If 100 grams of grape-sugar be given in a quarter of a litre of water or tea to a normal individual in the morning, fasting, an examination of the urine two or three hours subsequently will show that it has not given rise to glycosuria, but if, for any reason,

the metabolic functions of the pancreas are at fault a more or less marked reaction for sugar will be obtained. The production of alimentary glycosuria in this way does not, however, necessarily indicate that there is a gross lesion of the pancreas, for it may result from toxic changes such as are probably present in acute febrile diseases and alcoholism, and a similar result may be obtained in cases of neurasthenia, traumatic necrosis, acute diseases of the brain and meninges, in many forms of mental debility, especially mania and paralysis, in exophthalmic goitre, and in some diseases of the liver, not necessarily associated with obvious changes in the pancreas. The observations of Wille, however, show that in some 65 per cent. of cases in which alimentary glycosuria occurs a grave pancreatic disease is present. Many investigators have made use of cane-sugar in applying this test, but it is not so suitable for the purpose as dextrose, or fruit-sugar, as the results are not so simple and easy to interpret, for the glycosuria following the administration of cane-sugar may be due to anomalies of fermentation and absorption in the intestine.

(*b*) *Sahli's Test.*—This well-known method of diagnosis depends upon the fact that if iodoform be enclosed in gelatin capsules, hardened in formalin, and given by the mouth, it is almost unaffected by gastric digestion, but is readily dissolved by the pancreatic secretion. If therefore pancreatic digestion is normal, iodine should appear in the urine and saliva in from four to eight hours; the absence of the reaction, or its delayed appearance, if the motor functions of the stomach be normal, indicates, according to Sahli, an impairment of pancreatic digestion.

The great and apparently insurmountable difficulty in this method is to strike a degree of hardness for the capsules suitable in all cases. Formalin has the property of making all tissues on which it acts proof against digestion, tryptic as well as peptic, and it is therefore necessary

that the capsules should only be acted on long enough to protect them against digestion in the stomach, but not for a sufficient length of time to prevent their solution by the more active pancreatic secretions. This in itself is a difficult matter, but when it is remembered that normally there are individual variations in peptic and tryptic digestion the difficulty is still further increased. Experience has proved that these objections are not merely theoretical, for Fromme, Wallenfang, and Sahli himself have stated that, from a retarded reaction, the diagnosis of disturbed pancreatic function cannot always be made with certainty. A prompt reaction, however, appears to exclude any serious lesion of the gland. The results of Sahli's test have therefore only a negative value in diagnosis.

(*c*) *Test Meals.*—Since 1879, when Van den Valden drew attention to the fact that free hydrochloric acid was absent from the stomach contents in carcinoma of the pylorus, it has been recognised that a chemical examination of the gastric secretion was of considerable assistance in the diagnosis of malignant disease of the stomach. But in April, 1905, Moore, Alexander, Kelly, and Roaf extended this proposition by stating that an examination of the stomach contents, obtained about one hour after the administration of Ewald's test meal of a pint of tea without milk or sugar and a round of dry toast, showed striking diminution or entire absence of the hydrochloric acid normally present after such a meal, in cancer situated in other parts of the body, such as the breast, uterus, tongue, etc. Subsequent observers have not obtained quite such remarkable and constant results as those quoted by Moore and his fellow-workers in their original paper, but there is no doubt that a marked diminution in the amount of hydrochloric acid in the stomach contents is frequently met with in such cases, and that, taken in conjunction with other symptoms, it may often be of assistance in diagnosis.

The differentiation of malignant disease of the pancreas from chronic pancreatitis is, in some instances, so difficult that any method that holds promise of assistance is worthy of a careful trial. We have only had the opportunity of examining a test meal from three cases of cancer of the pancreas, and have obtained the following results:

Case I. (No. 662.)

Phloroglucin-vanillin reaction for free HCl	Negative
Total acid (as HCl)	0.007%
Physiologically active HCl	0.000%

Case II. (No. 749.)

Phloroglucin-vanillin reaction for free HCl	Negative
Total acid (as HCl)	0.05%
Physiologically active HCl	0.00%

Case III. (No. 780.)

Phloroglucin-vanillin reaction for free HCl	Negative
Total acid (as HCl)	0.009%
Physiologically active HCl	0.000%

It will thus be seen that not only was there absence of free hydrochloric acid in all these cases, but no evidence of physiologically active hydrochloric acid (as estimated by Willcox's method) could be found. For the sake of comparison we may quote another case, which, although the results of the "pancreatic reaction" pointed to simple inflammation, was so much like malignant disease, both clinically and at operation, that a guarded prognosis was given. The patient, however, rapidly improved after the operation and is now quite well:

Case IV. (No. 639.)

Phloroglucin-vanillin reaction for free HCl	Deep crimson
Total acid (as HCl)	0.13%
Physiologically active HCl	0.13%

In this instance there was an abundance of free hydrochloric acid, and the percentage of physiologically active

acid was not subnormal, in marked contrast to their entire absence in the other three cases. Our experience is as yet too small to permit of any dogmatic statement being made, but it is sufficient to show that the results of a chemical examination of a test meal, when taken in conjunction with other evidence, may prove of considerable help in diagnosis.

With such a number of signs and symptoms as those above enumerated it is difficult to understand how the idea has gained so firm a hold that disease of the pancreas is, as a rule, unrecognisable during life. Although, in any particular case, one may not meet with all of them, there is usually such a combination that, with care, no difficulty need be experienced in arriving at a satisfactory conclusion. Different diseases of the pancreas, as one would expect, present very various groupings of symptoms, but in all digestive, metabolic, and physical signs can be found that will indicate the true source of those alterations in well-being of which the patient complains. In every case the past history of the patient should be carefully gone into for evidence of chronic dyspepsia, gall-stone attacks, and recent infectious diseases, such as typhoid fever, influenza, etc., all of which may be followed by diseases of the pancreas. Then, having investigated the present condition of the case as regards loss of weight, alterations of appetite, especially an objection to meat and fat, nausea, vomiting, and pain in the upper abdominal region radiating under the left scapula, the presence or absence of jaundice should be noticed, particularly in the sclerotics, and the pancreatic region should be examined for a tumour and for tenderness on pressure. It should now be possible to determine whether the pancreas is probably diseased or not, and to decide whether the assistance of the clinical pathologist is required to further investigate the case.

In all cases of suspected pancreatic trouble it is advisable that a complete chemical and microscopical ex-

amination of the fæces and urine should be made by a competent observer, for the results of such examinations will, in the large majority of cases, clinch the diagnosis. The fæces should be examined as fresh as possible, for their reaction may quickly change, and the presence of an acid reaction is suggestive of pancreatic trouble. An excess of unabsorbed fat in the motions points to disease of the pancreas, particularly if this is chiefly due to a high proportion of neutral fat. Azotorrhœa, along with steatorrhœa, tends still further to confirm the diagnosis. Complete absence of stercobilin from the fæces is suggestive of malignant disease of the pancreas, while its presence points to obstruction of the common duct by gall-stones.

In investigating the urine a thorough examination should be made for albumin, sugar, acetone bodies, indican, bile, and urobilin; the urea, chlorides, and phosphates should be estimated quantitatively; and the centrifugalised deposit examined for calcium oxalate crystals. Sahli's test and Opie's test for fat-splitting ferments may be tried, and in all cases it is advisable to perform Cammidge's "pancreatic" reaction. The presence of sugar in the urine, along with evidence of disease of the pancreas, is of great value, and, even when sugar is absent naturally, its discovery after the administration of a test dose of 100 grams of glucose tends to confirm the diagnosis of disease of the pancreas. The acetone-bodies point to abnormal tissue waste, such as is met with in serious cases of pancreatitis and cancer of the pancreas, and an excessive amount of indican, although not diagnostic of disease of the pancreas, may indicate the site of the infection from which a chronic inflammation has arisen. Bile-pigments in the urine show that there is obstruction of the biliary passages, and a pathological excess of urobilin points to catarrh of the bile-duct, and possibly of the pancreatic duct, which may or may not be associated with a floating biliary

calculus. A diminished excretion of phosphates, when the patient is on a milk diet, is indicative of a pancreatic lesion, and a diminution of chlorides relative to urea is met with in serous effusions such as occur in malignant disease. A well-marked deposit of oxalate crystals tends to confirm a diagnosis of chronic pancreatitis. Sahli's test, when negative, is strongly against there being serious disturbance of the functions of the pancreas, and the presence of fat-splitting ferment in the urine probably indicates acute pancreatitis.

We have found the "pancreatic" reaction of very great assistance in all cases of suspected pancreatic disease, but we are not prepared to contend that it is pathognomonic or infallible, for even the most commonly relied upon tests are, it is well known, liable to prove misleading at times, unless due regard is paid to possible sources of fallacy, and the results are interpreted in the light of clinical evidence. As we have pointed out, it is not impossible that inflammatory and degenerative changes in other pentose-containing tissues of the body may at times give rise to a positive "pancreatic" reaction, but, having regard to the relatively large proportion of this substance contained in the pancreas, disease of that organ is the most likely, and probably the most common, cause of such a result. In making a diagnosis in suspected cases of pancreatic disease, or of jaundice in which it is sought to determine whether there is a gross obstruction to the free flow of bile and pancreatic juice into the intestine, and whether this obstruction, when present, is of a simple or malignant nature, it is important to remember that the "pancreatic" reaction is only one factor that has to be taken into account, and that, although it may afford valuable evidence, for or against, it is necessary that its indication should be considered with the clinical symptoms, and that, whenever possible, they should be checked by a chemical analysis of the fæces.

Finally, if there is a suspicion of malignant disease, Ewald's test breakfast may be given, and the stomach contents examined in an hour for free and physiologically active hydrochloric acid.

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CHAPTER XIII

INJURIES

The pancreas is more securely protected from direct violence than almost any other abdominal organ. Injuries are therefore comparatively rare, and, when they do occur, are almost invariably accompanied by more or less damage of other viscera. Garré was only able to

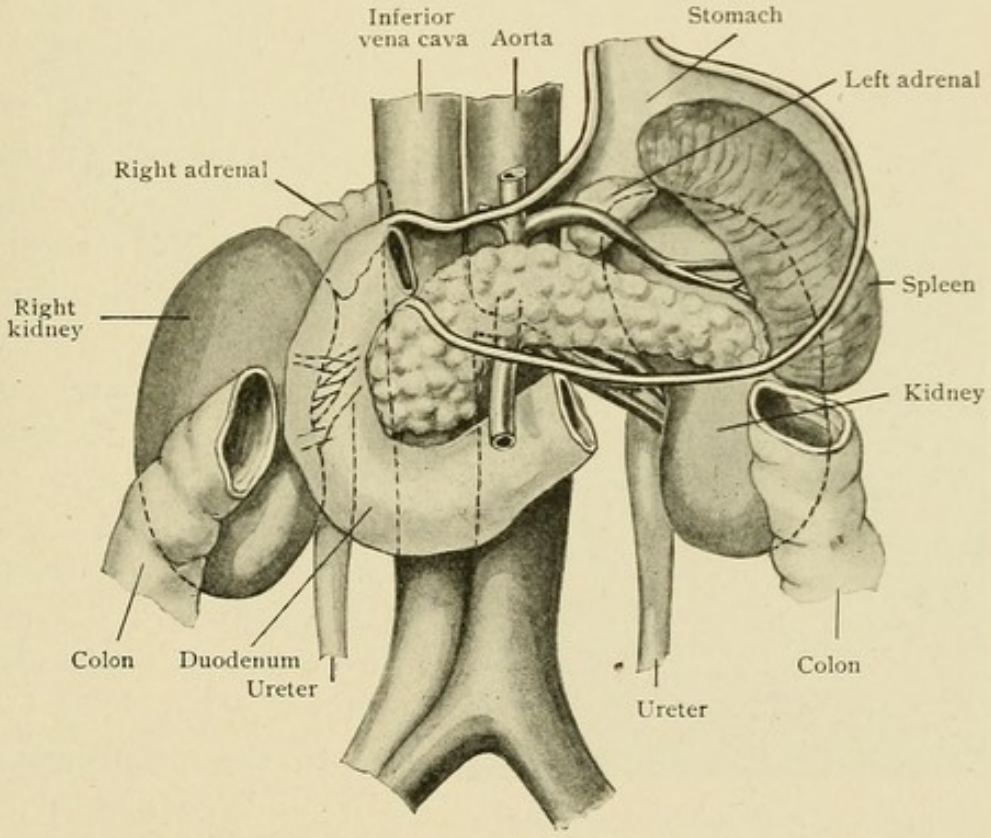

Fig. 115.—Diagram showing the relations of the pancreas.

meet with thirty recorded cases, and in but eight was the pancreas the only organ injured. Recovery occurred in three cases. In addition to the anterior wall of the abdomen, there lie in front of the pancreas the transverse

colon, the stomach, and the omentum, while behind are the aorta and inferior vena cava, the second lumbar vertebra, with the adjoining portions of the first and second vertebræ in the middle line, and the psoas and the quadratus lumborum muscles and the thick mass of the erector spinæ, with many fascial strata, laterally. The pancreas thus occupies almost the centre of the body, and any harmful influence coming from without must first encounter other more superficial structures.

Injuries of the pancreas may be divided into: (1) Lacerations due to direct violence; (2) bullet wounds; (3) penetrating wounds and stabs.

(1) LACERATIONS DUE TO DIRECT VIOLENCE

In the majority of these cases the force producing the injury has been directed from before backwards at the epigastrium, and has been of such severity that other organs within the abdominal cavity have been damaged at the same time. A rent in the liver, a tear of the kidney or spleen, a rupture of the duodeno-jejunal flexure or duodenum, a laceration of the stomach, or extensive injury to the peritoneum have all been observed. In most of the earlier recorded cases the injury to the pancreas was only recognised after death, and was accompanied by one or other of the lesions mentioned, but even in some of these the injury to the pancreas was so much greater

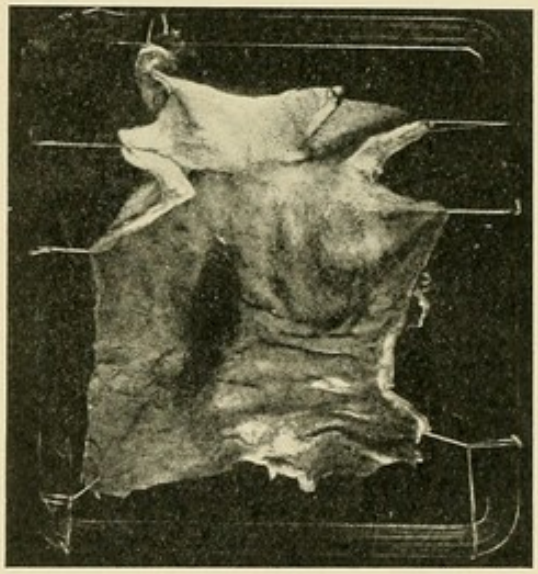

Fig. 116.—Traumatic rupture of the pancreas and bruising of the duodenum, followed by hæmatemesis and fat necrosis (Santos).

than that inflicted on other organs that it was probably the cause of the fatal issue. The number of recorded examples of injuries of the pancreas is probably not a correct indication of the frequency with which they occur, for when an injury of the gland forms only a part of a multiple visceral disorganisation due to violence it is apt

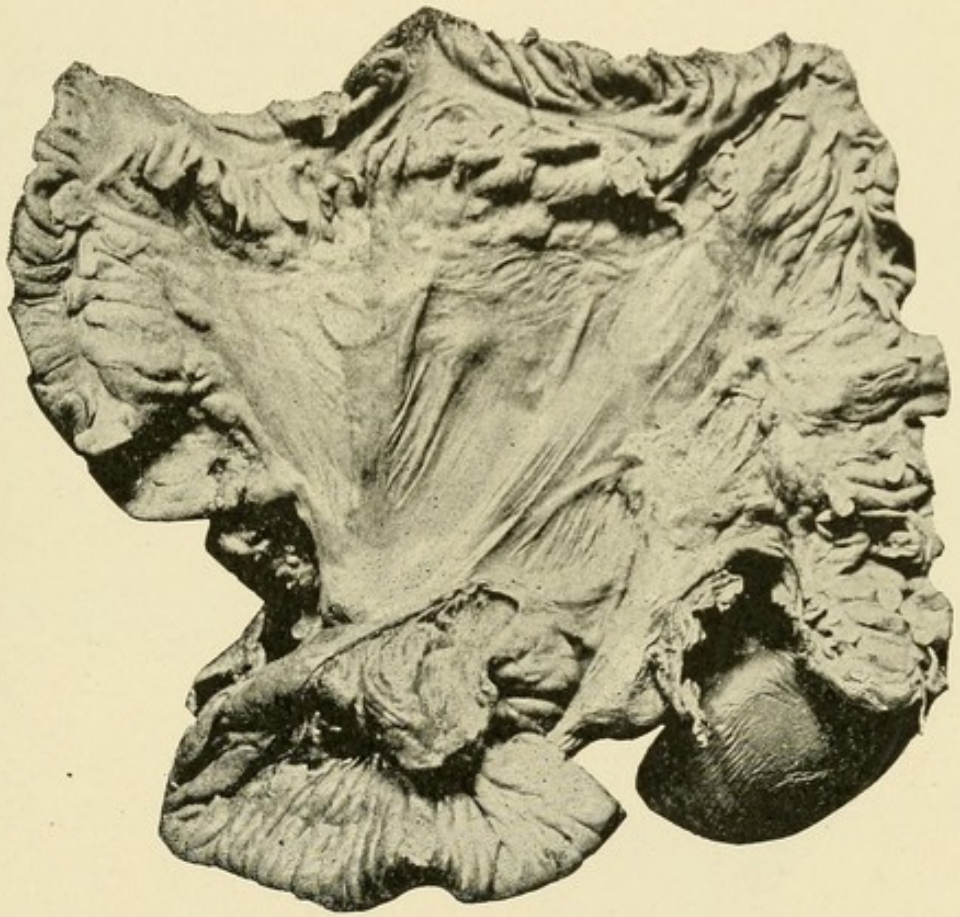

Fig. 117.—Showing the rupture in the duodenum. The ends have been filled with cotton-wool and separated from one another for the purpose of demonstration.

to be overlooked, even after death, as the hæmorrhage from a ruptured liver, spleen, or kidney is so profuse as to rapidly fill the peritoneal cavity.

Laceration of the pancreas is most commonly due to the patient being run over, and fatal cases arising from this cause have been reported by Travers, Stoerk, Cooper,

Pressel, and Hale White. In all of these the injury of the pancreas was accompanied by fracture or laceration of ribs, liver, kidneys, or other organs. In a fatal case recorded by Wilks and Moxon, however, where the pancreas was so crushed opposite the spinal column as to be

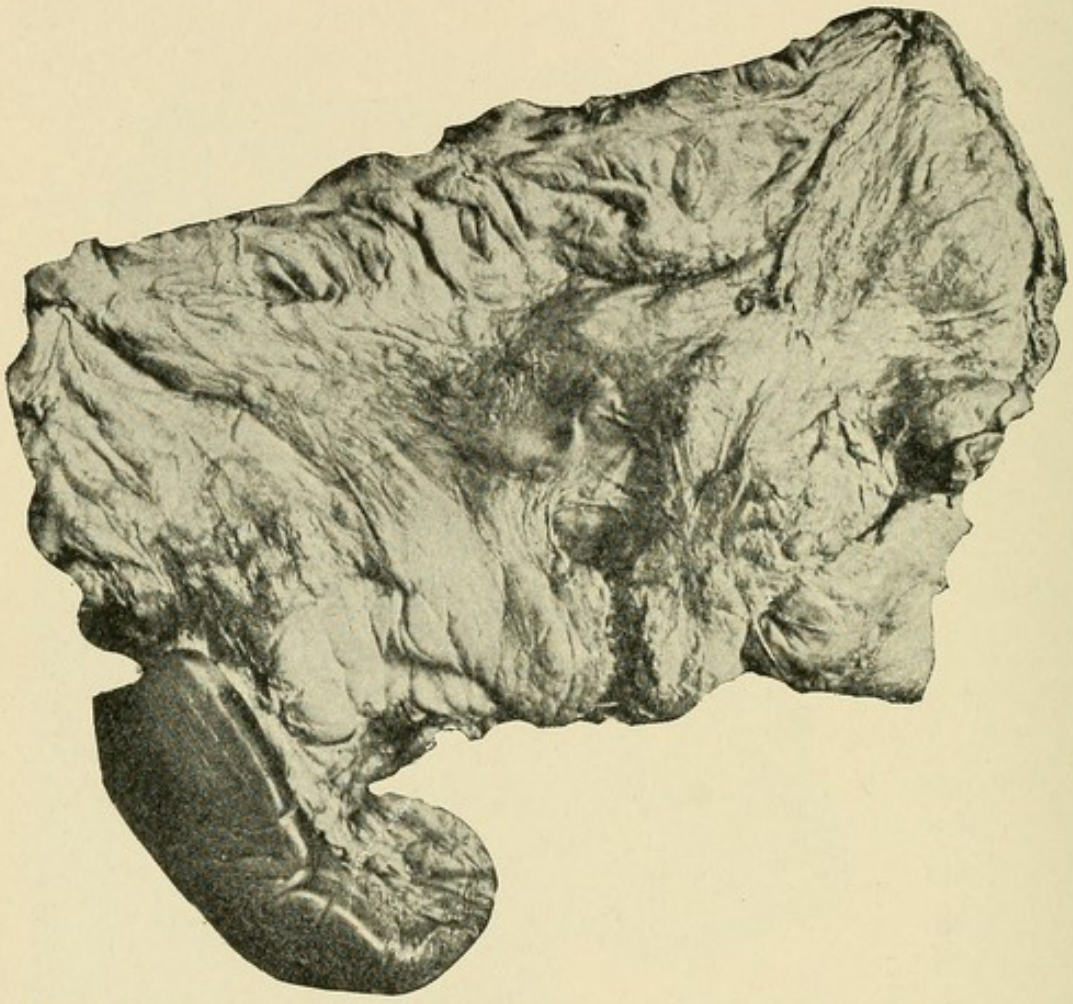

Fig. 118.—Shows the rupture in the pancreas and its peritoneal covering.

divided into two parts, the laceration was unaccompanied by other abdominal injuries, and the specimen shown in Fig. 119, from St. Bartholomew's Hospital Museum, was also taken from a patient in whom post-mortem the pancreas was the only organ found to be injured. In the latter case the patient had been crushed between two

vans, and on admission only complained of slight pain in the epigastrium. Twenty-four hours later he became collapsed, but recovered. Subsequently he vomited, became seriously collapsed, and died three days after the receipt of the injury. At autopsy a rupture of the pancreas dividing it into two nearly equal portions was found; there was fat necrosis in the neighbourhood, but no injury of the duodenum, liver, spleen, kidneys, or other abdominal viscera. Fatal cases of laceration of the pancreas following a kick have been described by Jaun,

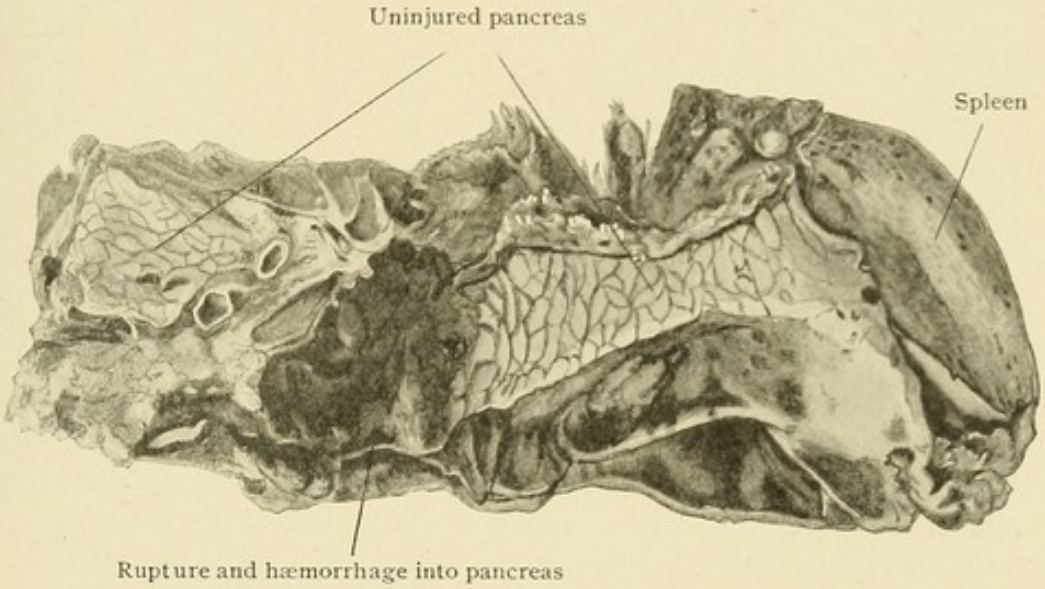

Fig. 119.—Rupture of the pancreas, without any other abdominal injury (St. Bartholomew's Hosp. Museum, 2276 D).

Leith, and Groeningen. In Jaun's case there was no other abdominal injury. An injury of the pancreas that caused death on the fourth day was produced, in a case reported by Wagstaff, by a fall from a cart on to the left side. Post-mortem the other abdominal viscera were found to be uninjured. Goldmann, Villiers, and Hale White have reported instances in which fatal injury of the pancreas, accompanied by more or less extensive damage of other abdominal organs, has followed a blow in the upper epigastric region. In most instances the

chief injury has been opposite the spinal column, the pancreas being probably caught and compressed thereon by the crushing force.

Although injury of the pancreas is usually brought about by severe violence, the tissues of the gland are so soft and easily bruised that slight injuries have more effect upon it than upon firmer organs. The following case, observed by one of us, illustrates the serious results that may follow from a comparatively slight blow over the region of the pancreas:

A butler slipped and fell forward against a knifeboard projecting from the end of the table at which he was working. The blow was comparatively slight and the man did not even fall to the ground. Pancreatitis followed on what was, at the beginning, probably a mere bruising of the pancreas, but which was succeeded by slight bleeding into the gland, and, this effusion becoming infected, acute hæmorrhagic pancreatitis resulted. An exploration for the cause of the pancreatitis resulted in the discovery of a large collection of highly blood-stained fluid in the lesser peritoneal sac, some of which had burst through a small laceration in the omentum into the greater peritoneal sac. There was general peritonitis present at the time of operation, and though drainage was freely adopted, both from the front and back, the patient did not survive many hours.

A case of considerable interest and importance has been described[1] in which pressure from a tourniquet caused severe bruising of the pancreas. The patient had an aneurysm of the abdominal aorta, not far from its bifurcation, and an attempt was made to treat it by the application of a tourniquet nearer the heart. In the few hours during which the patient survived the application of the instrument, no symptoms referable to the pancreas were observed, but post-mortem the gland was found to be much bruised where it lay across the vertebral column.

[1] Lancet, Feb. 4. 1905.

In a second class of injuries due to crushes and blows, although the pancreatic lesion is less profound than in those just referred to, it is the main result of the injury, and slowly gives rise to symptoms that may be relieved by operation. After the shock of the accident has passed off, the patient may appear to have quite recovered, but in a longer or shorter time, varying from a few days to several weeks, an abdominal tumour appears, which on being explored proves to be a distension of the lesser sac by blood-stained fluid. The first case of this kind was recorded by Külenkampff, and others have been reported by Senn, Küster, Karewski, etc. Cases following a blow have been described by Ross, Hadra, Lloyd, Randall, Karewski, and one of us, by Littlewood after a kick, by W. H. Brown after a crush, and by Cathcart and Sheen after the patients had been run over. Coombs and Nash have tabulated the records of twenty-five cases, including a few in which the swelling has followed vomiting or some other form of straining. "The sequence of events in such cases is probably that the traumatism causes a laceration of the posterior layer of the lesser sac and of the pancreas, to which it is intimately adherent. Blood, and possibly some pancreatic secretion, are then poured into the lesser sac and peritonitis results. The foramen of Winslow is sealed by adhesion, and the lesser cavity of the peritoneum, now a closed sac, is distended with serous fluid mixed with blood and pancreatic secretion. When the fluid is evacuated the pancreas continues to pour its secretion into the lesser sac through the rent in its peritoneal investment." (Mayo Robson and Moynihan, p. 51.) The relation of these tumours to the pancreas, and the presence in their contents, and in the fluid issuing from the drainage-tube, of ferments, has led to their being generally spoken of as pancreatic cysts, but they are now regarded as one of the varieties of pseudo-cysts of the pancreas, and will be considered in that connection in a subsequent chapter.

Symptoms and Diagnosis.—In the first class of cases, where the injury to the pancreas is great, but, as a rule, only constitutes one of the results of the accident, there has been profound collapse coming on rapidly or, as in the cases reported by Jaun, Wagstaff, and Leith, after an interval of an hour or more. The immediate symptoms of shock are due to the hæmorrhage, but when they appear after a latent interval are to be ascribed to the complications arising from the injury to the pancreas. According to Leith, the absence of all external signs of injury of the abdomen is surprising and noteworthy. The absence of any definite signs pointing to pancreatic injury renders an accurate diagnosis impossible in such cases, and it has usually only been at the post-mortem examination that the source of the hæmorrhage, etc., have been traced. When, however, from the gravity of the collapse, the site of the injury, and the presence of dulness in the right or left flank, it is evident that there is some serious visceral lesion with internal hæmorrhage, speedy operation is indicated, and may prove successful in saving the patient's life, even when there is extensive laceration of the pancreas, as in the case recorded by Randall.

Where the symptoms of shock are less severe, and the patient recovers, but later develops a cystic swelling in the region of the pancreas, the diagnosis is less difficult, and operation may be undertaken with every prospect of a successful issue. The nature of the contents of such a cystic swelling may afford evidence of its origin from an injury of the pancreas by the discovery of ferments. The fluid may be clear, or turbid from the presence of blood, and is alkaline in reaction. It has a specific gravity of 1.010 to 1.0120, and usually contains albumin and nucleo-proteids. Starch-splitting and fat-splitting ferments are present, and can be recognised by the tests described on page 264. As a rule, it has no digestive

power for proteids, for it has not been activated by contact with enterokinase, but feeble proteolytic powers may be shown, such as are possessed by the juices of many tissues. The accelerating action of salts of calcium, etc., on the proteolytic activities of pancreatic juice, demonstrated by Delezenne, may account for the presence of a more marked digestive power in some instances. Where the swelling forms quickly, direct laceration of the pancreas is indicated, but where it forms slowly, may be after some months or even years, it is probably due to pancreatitis following the injury, with effusion into the lesser sac. The appearance of a swelling which rapidly reaches a certain bulk, and then remains stationary, suggests the outpouring of fluid into a preformed sac produced by closure of the foramen of Winslow by adhesions previous to the injury. The swelling occupies the epigastric, umbilical, and left hypochondriac regions. The stomach and transverse colon can be detected in front, and the descending colon behind and to the left.

Treatment.—The immediate shock and collapse consequent on the accident having been treated by the means usually adopted in such cases, a satisfactory reaction on the part of the patient raises the question of operative interference. Where there is evidence of internal hæmorrhage this should be undertaken at once, and an attempt made to secure the bleeding points. Experimental work has shown that wounds of the pancreas can be sutured, and that healing speedily takes place, so that if a laceration of the gland be found it should be dealt with by accurately coapting the edges by sutures, care being taken, however, to avoid puncturing the main duct of the gland. The cases in which such surgical intervention is possible are, unfortunately, few, as the injury to the pancreas is most frequently only part of a wide-spread destruction involving the liver, kidneys, spleen, stomach, or intestine. In the case reported by

Randall, referred to previously, operation six hours after the accident was followed by recovery.

The patient had been crushed between the pole of a van and another vehicle in the epigastric region. He had violent pain, became faint and collapsed, and vomited. On admission to hospital an hour later, he was found to be still collapsed, with a small weak pulse of 90 and a temperature of 95° F. He was treated with stimulants, warmth, and a hypodermic injection of half a grain of morphin. Midway between the ensiform cartilage and the umbilicus there was a bruise nearly two inches in diameter and very tender to the touch. The abdomen moved with respiration, but was very tender, especially above the navel. The liver dulness was normal, but there was marked dulness in the right flank. The urine showed no abnormality. At the operation no gas was found in the peritoneum, but there was much clotted and fluid blood. No lesion of the liver, stomach, or bowels could be found. A large tear, directed vertically, and running from the stomach to the liver, was seen in the gastrohepatic omentum, and there was a tear in the peritoneum over the pancreas. Under this was a tear in the body of the gland two inches long, running from the right and below upwards and to the left, leaving a loose, tongue-like process of gland substance, the base of which was half the width of the organ. On passing a finger through the tear it came directly upon the aorta. There was free oozing, but no large blood-vessels could be found. The rent in the pancreas was sewn up by four silk stitches, and, after the lesser peritoneal sac had been cleansed, the greater part of the tear in the gastro-hepatic omentum was sewn up with a continuous catgut suture, space being left for drainage. The abdomen having been thoroughly flushed with hot saline solution, an iodoform gauze packing was inserted down to the pancreas and the rest of the abdominal wound closed. For the first three days the patient was constantly sick and in much pain. He later developed delusions, but slowly recovered, gaining in weight and strength, and was discharged, ten weeks after the operation, with the wound healed. On one occasion the urine contained a small quantity of

sugar, but it quickly disappeared. No special features were noticed in the motions. The discharge from the wound consisted of a viscid, slightly turbid fluid, which caused excoriation of the margins of the wound. A fortnight after the operation it was noticed that the skin over the abdomen and lower part of the thorax resembled that produced by an extensive burn of the first and third degrees.

A somewhat similar case in which recovery followed prompt operation has been reported by Karewski. The patient had been run over after being struck in the abdomen by the shaft of a vehicle. He was able to walk home, but abdominal pain coming on shortly afterwards an exploratory laparotomy was performed. There was a large quantity of blood, especially in the region of the gastrocolic ligament, and the head of the pancreas was found to be crushed. The patient lost 400 grams of pure pancreatic juice daily through the fistula and diminished in weight, but the secretion diminished on a fatty antidiabetic diet and the fistula was eventually closed.

The treatment of the cystic swellings following injury of the gland will be discussed under Cysts of the Pancreas.

(2) BULLET WOUNDS

Cases of bullet wounds of the pancreas have been described by Otis, Sanitas, Niemann, Bertram, Von Bramann, Hahn, Nini, Borchardt, Simmonds, Mann, Körte, Slavsky, Carnell, Jephson, Becker, and Kindt. Rarely the pancreas has been the only abdominal organ injured, but in the majority of instances other organs have also been involved in the injury. Otis, in his surgical report on the American Civil War, relates three cases. In one the pancreas and spleen were both lacerated, and the splenic artery was divided. The patient lived a month. In the second the patient lived fifteen days, and the stomach, as well as the pancreas, was found to have been

wounded. In the third the lung, the liver, and the pancreas were all injured. The patient lived but twelve days. The late President McKinley was wounded in the stomach, pancreas, and left kidney. Ninni reports a case of revolver wound of the abdomen in which there was a wound of the pancreas, six of the small intestine, and one in the colon at the hepatic flexure, but in which the patient recovered after operation, and left the hospital thirty-five days after admission. In a case of revolver wound of the pancreas, associated with double perforation of the stomach, recorded by Kindt, widely disseminated fat necrosis was found post-mortem, and a similar condition has also been noted in two other cases after death, but has not been recorded as present in any of the cases at operation. The organ most commonly injured with the pancreas has been the stomach (nine cases), then the liver (seven cases), the lesser omentum (four cases), the diaphragm (three cases), the spleen, small intestine, and large intestine each in two, and the lung, kidney, heart, and portal vein each in one instance.

Symptoms.—There are no pathognomonic signs of injury of the pancreas in bullet wounds of the abdomen, and even suggestive symptoms are usually absent. The probable course of the bullet, as indicated by the site of entry and exit, is usually the only guide. When the abdomen is opened and neighbouring viscera are found to be wounded, particularly the posterior wall of the stomach and lesser omentum, it is essential that a careful search should be made for any injury of the pancreas.

Treatment.—Operation should be undertaken as speedily as possible in all cases. Any bleeding points should be secured, and a careful but rapid search made for injury to the stomach, intestine, liver, etc. The wound of the pancreas may be sutured, but, if there is much laceration, it may be necessary to resect a portion of the gland and unite the clean-cut edges by sutures. Care

must be taken to avoid the main duct, the superior mesenteric artery, and the portal vein. Complete disorganization of the gland can only be treated by plugging and drainage, for it is practically impossible to remove it, and the attempt is not justifiable on physiological grounds. Where suture is possible drainage should always be adopted, for there is invariably a certain amount of leakage, and if an exit is not provided for the exuding secretion, local disturbances and peritonitis may result. It is noteworthy that in two cases where an injury of the pancreas was sutured, but no drainage was provided, a localised destruction of tissue was found post-mortem. Drainage has usually been provided through the abdominal wound, but a posterior opening, such as Jephson adopted in his case, and was also carried out by one of us in another instance, is probably more efficient. It is frequently stated that wounds of the pancreas are almost always fatal, but this is not necessarily the case, if suitable operative measures are quickly taken. Of the twenty-one cases of injury of the pancreas due to gunshot wounds of which we have found records, fifteen were operated on and nine of these recovered (Bramann—two, Hahn, Nini, Borchardt, Slavsky, Jephson, Otis, and Becker). Of the six in which death occurred, the injury of the pancreas was not discovered in three, so that in nine out of twelve instances it may be considered that the operation saved the patient's life, for all but one of the cases in which operation was not resorted to died.

(3) PENETRATING WOUNDS

Penetrating wounds due to stabs or cuts with a knife or bayonet have been reported by Kleburg, Laborderie, Caldwell, Dargau, and Küttner. In the cases described by all but Küttner, the pancreas protruded through the wound, and was either returned or the projecting portion removed. Recovery followed in all. In Küttner's case

there was an abdominal wound, 14 cm. long, through which protruded the stomach, transverse colon, and several loops of small intestine. At the operation, a quarter of an hour after the receipt of the injury, the anterior wall of the stomach was found to have been injured, the left border of the liver was notched, the lesser omentum was cut, and the pancreas had been transfixed just to the left of the tuber omentale. Venous and arterial blood were welling up from the wound in the pancreas, but this was checked by two deep and one superficial catgut suture in the parenchyma of the gland. The bursa omentalis was plugged and the stomach wound sutured. The patient recovered, although, at first, he was gravely ill with symptoms of threatened collapse and subphrenic abscess.

Treatment.—The treatment of penetrating wounds of the pancreas is exactly on the same lines as those described for gunshot wounds, and what has been said under that heading equally applies here.

SEQUELÆ

The sequelæ of injuries of the pancreas may be seen in the gland itself, or are shown by changes in the neighbouring tissues. The effects produced by injury of the pancreas, with closure of the foramen of Winslow, and the conversion of the lesser peritoneal sac into a cystic cavity, have already been referred to. The injury may also produce a true cyst of the pancreas, either from bruising and tearing of the duct, causing stenosis and an accumulation of secretion behind the point of injury, or the duct may be compressed and distorted by the scar tissue resulting from the injury to the neighbouring gland substance. Cases in which inflammatory changes in the gland have resulted from injury have been recorded by Wandesleben, Rolleston, and others. In Rolleston's case an abscess in the head of the pancreas, with fat

necrosis in the subperitoneal cavity, was found at the post-mortem, eighty days after a blow in the abdomen which had given rise to pain, vomiting, inaction of the bowels, and collapse simulating intestinal obstruction. Hansemann, Fitz, and Prince have described cases of necrosis of the pancreas after injury. A wound of the abdominal wall has, in some cases, been followed by protrusion of the pancreas. The possibility of such an occurrence has been doubted, but there is now indisputable evidence that such a complication may occur. The original case of "prolapse of the pancreas" recorded by Laborderie was proved by microscopical examination of the protruding tissue to be in reality a case of prolapsed omentum, but well authenticated cases have been since reported by Otis (two), Kleberg, Caldwell, Dargau, Allen, Thompson, and Pereira-Guimaraes. The failure of Laborderie to recognise the nature of the tissue in his case by naked-eye inspection emphasises the necessity of a careful microscopical examination in every instance.

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CHAPTER XIV

INFLAMMATORY AFFECTIONS OF THE PANCREAS

Catarrh and Suppurative Catarrh of the Pancreas

If we were to base our opinions on the post-mortem records of the past, inflammatory affections of the pancreas would have to be reckoned among the rarest of diseases, but recent clinical observations and operative experience show that such conclusions would be far from accurate, and that inflammatory affections of the pan-

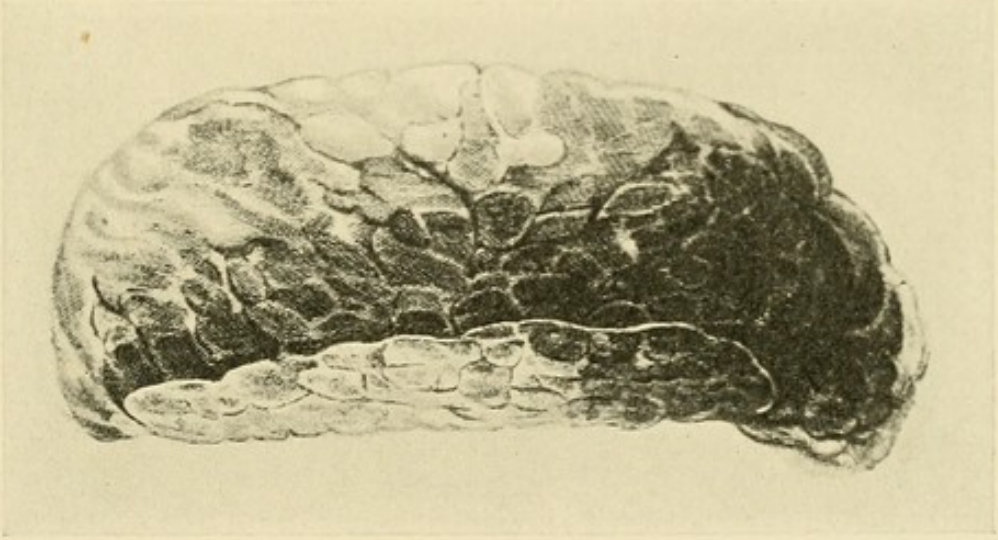


Fig. 120.—"Enlarged and hard pancreas"—probably a case of chronic pancreatitis (Baillie).

creas, or its ducts, are very much more common than is generally supposed.

Historical References.—When studying the subject of pancreatitis, in the light of modern pathological knowledge, it behoves us to bear in mind that the older pathologists had noticed and described the naked-eye appear-

ances of nearly all the conditions that are engaging so much of our attention at the present time. Tulpius, so far back as 1672, describes a diffuse pancreatitic abscess of pyæmic origin, and Matthew Baillie, physician to St. George's Hospital, in a work on "Morbid Anatomy," published in 1799, describes what he calls a hard pancreas with the lobules distinct, but which is what we now should call a case of chronic interstitial pancreatitis. He also figures in the same volume a case of pancreatic calculi, most carefully dissected, showing the relation of the bile and pancreatic ducts. Portal in 1804 described a case of acute suppurative pancreatitis following on an attack of gout in the feet, and Percival, in 1818, described a well-marked case of pancreatic abscess associated with jaundice. The following is a quotation from a paper by Dr. W. J. Mayo before the American Surgical Association, the executive committee of which approved of it for publication: "Balzer in 1879 first described acute pancreatitis with fat necrosis. Little attention was attracted to the subject, however, and it was not until Fitz ten years later wrote his classical papers that the medical world really became aware of the inflammatory diseases of the pancreas. Fitz soon after pointed out the fact that many supposed cysts of the pancreas due to traumatism were really accumulations of fluid in the lesser cavity of the peritoneum and the omental bursæ. A proper understanding of chronic pancreatitis has been largely due to Robson, who first noticed the disease in connexion with his operative work upon the biliary tract. In fact, the surgical study of the inflammatory diseases of the pancreas may be said to be the result of an inquiry into the causation of some of the complications of gall-stone disease."

Classification.—Pancreatic inflammations may be catarrhal, in which the inflammatory trouble is in the ducts, or parenchymatous, in which the substance of the pancreas

is involved. The former resemble the different forms of cholangitis, with which, indeed, they are frequently associated; the latter bear more resemblance to inflammatory affections of the appendix, "suppurative and gangrenous appendicitis." The following shows the classification at a glance:

(A) Catarrhal Inflammations:

(*a*) Simple catarrh { acute. / chronic.

(*b*) Suppurative catarrh.

(*c*) Pancreo-lithic catarrh.

(B) Parenchymatous Inflammations:

Acute:

(*a*) Hæmorrhagic pancreatitis.

1. Ultra-acute, in which the hæmorrhage precedes the inflammation, the bleeding being profuse, and both within and outside the gland.
2. Acute, in which inflammation precedes the hæmorrhage, which is less profuse and is distributed in patches through the gland.

(*b*) Gangrenous pancreatitis.

(*c*) Suppurative pancreatitis (diffuse suppuration).

Subacute:

Abscess of the pancreas (not diffuse suppuration).

Chronic:

(*a*) Interstitial pancreatitis.

1. Interlobular.
2. Interacinar.

(*b*) Cirrhosis of the pancreas.

Etiology.—The etiology of pancreatitis may be classified under predisposing and exciting causes.

Among the predisposing causes are:

(*a*) Obstruction in the ducts, the result of gall-stones, duodenal catarrh, pancreatic calculi, cancer of the papilla or of the head of the pancreas, ulcer of the duodenum, followed by cicatricial stenosis of the papilla, ascarides and lumbrici, etc.

(*b*) Injury either from a bruise, as by manipulation in operating, or from a crush, as by a blow in the epigastrium, or from wounding by a sharp instrument.

(*c*) Hæmorrhage into the gland.

(*d*) General ailments, such as typhoid fever, influenza, and mumps.

(*e*) Certain anatomical peculiarities in the pancreas or its ducts.

(*f*) Atheroma, or fatty degeneration, of the blood-vessels. Back-pressure from disease of the heart, lungs, etc.

(*g*) New-growth, *e. g.*, cancer or sarcoma.

The chief exciting causes are:

1. Infection conveyed:
   (*a*) From the blood, as in syphilis or pyæmia.
   (*b*) From the duodenum, as in gall-stone obstruction or gastro-intestinal catarrh.
   (*c*) By extension inwards from adjoining organs, as in gastric ulcer or cancer eroding the pancreas.
2. Irritation, as in alcoholism (doubtful).

The anatomy of the pancreas, with its ducts opening into a portion of the intestine never free from organisms, is the key to the etiology of pancreatitis, but even so, were it not that the common bile-duct and the pancreatic duct are so closely related the pancreas would probably generally escape. It is well known that even aseptic

ligature of the common bile-duct opens the way to the presence of organisms within the bile-ducts, and we have very definite proof that a gall-stone in the common duct is very shortly followed by infective cholangitis, which may, in unfavourable circumstances, become suppurative cholangitis and lead to abscesses in the liver or to other secondary troubles. But in 28.5 per cent. of cases (Testut) the common bile and pancreatic ducts open together into the ampulla of Vater, which itself opens into the duodenum, and, according to Helly, in 62 per cent. of cases the common bile-duct is intimately embraced by the pancreas, so that when a gall-stone passes down the bile-duct it must, of necessity, in a large proportion of cases, compress the pancreatic duct and cause a damming back of its secretion, which, arguing from analogy as well as from practical experience of the troubles that follow, means damming back an infected secretion. Thus it is brought about that in many cases of common-duct cholelithiasis, where the calculus reaches the pancreatic portion of the duct, and remains there for some time, catarrhal inflammation of the pancreas occurs. If the stone passes after a short period the pancreatitis may subside and leave no trace, or the swelling of the pancreas may persist and, for a time, keep up pressure on the common bile-duct, leading to a persistence of the jaundice, though there is no concretion left to cause obstruction, nor any evidence of disease of the liver beyond the jaundice due to the mechanical obstruction. Thus may be explained some of the cases of chronic jaundice with so-called biliary catarrh.

If, however, the gall-stone obstruction persists for some time, and the patient's health is feeble or becomes seriously deteriorated, what was at first merely a simple catarrh may become a suppurative one, and as the same process involves the liver and the pancreas the ducts of both become filled with pus. We have now suppurative

catarrh of the pancreatic ducts associated with a suppurative cholangitis, a very serious, and generally a fatal, condition.

If the suppurative catarrh persists unrelieved, it may lead, not only to abscesses in the liver, but also to abscesses in the pancreas, and possibly, in case of survival, to subacute pancreatitis, as in cases to be described under abscess of the pancreas. If the suppurative catarrh takes on an acute course the condition may become one allied to, and unrecognisable from, pyæmia, as in a case to be related later.

If the infective catarrhal condition persists, and does not assume the more dangerous suppurative form, or even if simple obstruction of the pancreatic duct persists from any cause with only mild infection, we may have an almost analogous condition to the one occurring in the liver that produces cirrhosis. In this more chronic form interstitial pancreatitis occurs, which in an early stage may be arrested by the removal of the cause, as will be shown when considering chronic pancreatitis. The chronic pancreatitis is of the interlobular variety, and consequently does not involve the islands of Langerhans until a late stage, when the organ may become cirrhotic and diabetes supervenes.

If a small gall-stone happens to descend into an unusually large diverticulum of Vater and to lodge there, it will make a through channel from the common bile-duct, as shown in the diagram (Figs. 60 and 61), and this Opie has shown to be a cause of acute pancreatitis, the bile being forced direct into the pancreas. In one case under the care of Dr. Halsted this condition occurred and acute hæmorrhagic pancreatitis ensued. Opie states that he has produced acute hæmorrhagic pancreatitis in dogs by injecting bile into the pancreatic duct. Other irritating substances, suspensions of bacteria, and various acids and alkalies have the same effect, and have been considered in detail in the chapter on pathology.

It is quite clear, therefore, that gall-stones in the common duct are a frequent, in fact, by far the most frequent, cause of the various forms of pancreatitis, but the anatomical conditions just mentioned, though evidently potent, are certainly not necessary for the production of acute pancreatitis, which may, as is well known, occur apart from cholelithiasis. Any gall-stone or stones impacted in the pancreatic portion of the duct, or even filling the ampulla of Vater, may be efficient causes of the trouble.

It may be asked, Why should not every case of common duct cholelithiasis be complicated by pancreatic inflammation? This is readily explained by the fact that in a certain percentage of cases the common bile-duct and the pancreatic duct open by separate orifices into the duodenum, while in another percentage the duct of Santorini is either the principal outlet for the pancreatic secretion or is of such a size that it can act as an efficient outlet even if Wirsung's duct becomes obstructed. The condition described by Opie, where the ampulla of Vater is very large and a small gall-stone becomes impacted at its orifice, is only rarely found; otherwise acute pancreatitis would be more common owing to overwhelming of the pancreatic ducts by infected bile.

Besides gall-stones the other factors mentioned may lead to obstruction of the pancreatic ducts, to infection of the pent-up secretion, and to the different varieties of pancreatitis, the *rationale* of the process being similar to the one sketched above. It is possible that infection may extend upwards from the duodenum without preliminary obstruction, apparently by continuity of mucous membrane, catarrhal pancreatitis being then a sequel of gastro-duodenal catarrh.

In case of injury, in whatever way inflicted, it seems not unreasonable to think that the soft glandular substance will readily yield and so set free the auto-destruc-

tive secretion of the gland, which by dissolving the walls of the blood-vessels will lead to further hæmorrhage, and then to the collection of a quantity of easily decomposable material that only needs infecting to become acutely dangerous. The contiguity of the stomach and intestines furnishes the possibility of infection, though if infection does not take place the injury may be repaired as in other organs. This probably explains acute pancreatitis supervening not immediately but some days after an injury.

Hæmorrhage into the pancreas, so-called pancreatic apoplexy, arising from diseased vessels, or in some other way, by disrupting the gland, may lead to pancreatitis, as in the case recently reported to the Société de Chirurgie by M. Guinard.[1] That hæmorrhage into the pancreas does not always give rise to pancreatitis is shown by the presence of old blood-stains in cases dying from other causes, and it is reasonable to argue that some other factor is necessary. M. Guinard is of opinion that in his case the mercurial treatment played a part in the etiology of the condition, for, just as mercury produces salivation, it is possible that it may act upon the pancreas in an

[1] A man aged thirty-five, for several days had been relieved by injections of the benzoate of mercury for a specific orchitis. After the tenth injection he suddenly felt a sharp stabbing pain in the epigastric region; it was so acute that several hypodermics of morphine failed to give relief. During the following days the patient had fetid diarrhœa, and a small tumour appeared in the epigastric region. It was diagnosed as a gumma, and the mercurial infections were continued; but the patient continued to have great pain, with continued diarrhœa and complete intolerance for food; he lost flesh to an alarming extent, and became cachectic. When M. Guinard was called in he found him almost moribund. To the left of the linea alba, between the umbilicus and the costal margin, there was a tumour of the size of a man's fist, smooth, shining, almost fluctuating, dullish on percussion. An exploratory puncture gave issue to sticky blood. From the sudden onset of the attack, the intense pain, the rapid cachexia, and the absence of fever, M. Guinard diagnosed hæmorrhagic pancreatitis, and performed laparotomy. He found a large blackish retrogastric tumour, from which on incision a large quantity of fluid blood mixed with clots escaped. It was a hæmatic cyst of the pancreas. A drain was put in, and cure was rapid. On awakening from the anæsthetic the epigastric pains had disappeared. The contents of the cyst were found to be absolutely aseptic.

analogous way, giving rise to mercurial pancreatism with intense congestion of the gland and interstitial hæmorrhage. It has also to be remembered that the patient was a syphilitic subject. Infection of the disorganised tissues probably plays an important part in the conversion of a simple hæmorrhage into the acute fulminating inflammatory condition in many instances, and the amount and situation of the blood have also, no doubt, an important influence on the result.

In general ailments, such as typhoid fever, influenza, etc., the well-known predilection of typhoid bacilli for the biliary passages would afford an easy explanation of their access to the pancreas, and, though it is difficult to prove, in several cases of catarrhal inflammation of the pancreas a history pointing strongly to influenza and to typhoid fever as the cause has been obtained. In one case the relationship was proved by the discovery of typhoid bacilli.

As to mumps and pancreatitis there seems to be some peculiar and intimate relationship between the salivary glands of the mouth and the abdomen, and in the case of a young adult coming under the observation of one of us some years ago, it seemed highly probable that a metastasis occurred about the third day of the disease, when the pain and distress almost completely left the face and were followed by violent epigastric pain and alarming symptoms of depression, accompanied by sickness and fever, which then rapidly passed off, after three days' anxiety, and were followed by orchitis. M. Simonin gave the result of his observations on 652 cases of mumps treated in the military hospital of Val de Grâce. In ten cases, or 1.3 per cent., there were symptoms of pancreatitis which occurred from the first to the twelfth day of the disease and lasted from two to seven days, the principal symptom being epigastric pain and tenderness, with sickness and vomiting.

Auche has reported two cases of pancreatitis complicating mumps.

The first was in a lad, aged twelve years, who woke during the third night of his illness complaining of pain in the epigastrium of a continuous nature, with exacerbations; in half an hour vomiting occurred, at first of food, later of bile. The pain was confined to the epigastrium, midway between the umbilicus and xiphoid cartilage, extending as far as the left costal arch. Owing to the tenderness it was impossible to ascertain if there was any intra-abdominal swelling. During the ensuing day the pain was slightly less, the exacerbations were less frequent. Vomiting occurred four or five times, but only on taking fluids. The bowels acted once; the motion looked as if it did not contain fat. Next day, the fifth since the parotid glands were swollen, the pain was still less, and less frequent, but it was sufficiently severe to prevent deep palpation; a motion passed was normal, as was also the urine. Bilious vomiting continued. Next day, the third since the onset of abdominal symptoms, vomiting ceased, and liquid food was well borne. On the fourth day no swelling could be felt on deep palpation. The temperature had fallen from 38.9° C. to 36.8° C. On the fifth day the patient seemed perfectly recovered.

The second case was a boy, aged nine years. On the fifth day of an attack of mumps, suddenly epigastric pain and vomiting supervened. Next day pain and vomiting continued. When these symptoms had lasted three days the patient was seen for the first time; the pain was limited to the left side of the epigastrium, vomiting had occurred once during the day, the liver could be felt below the costal arch. Calomel was ordered. The patient was only seen once.

A similar case, also in a boy, has been described by Jacob. In this instance pain in the abdomen was complained of on the fourth day of the disease, and on examination a tender swelling was found in the epigastrium. The first case in which a post-mortem examination had been made was described by Lemoine and Lapasset in 1905.

In this case a soldier, a native of Algiers, aged nineteen years, was admitted into hospital on October 2, 1902, suffering from mumps. The only previous illness was malarial fever. The case ran a benign course, the temperature not rising above 100.2° F. and becoming normal on the fifth day. On the eighth day the illness appeared to have terminated, but on the evening of the tenth day there was a rigor with a rise of temperature to 103.8° and pain and swelling in the right testicle. The orchitis rapidly subsided, the temperature became normal on the fourteenth day, and the patient was again pronounced convalescent, but when visited on the morning of the fifteenth day he complained that he had not slept and that he vomited several times during the night. Although the temperature was normal he appeared to be prostrated. The conjunctivæ showed a slightly icteric tinge. The upper abdomen was tender, especially in the epigastrium and the region of the gall-bladder. Here the patient had a feeling of weight. The spleen was enlarged and tender. The pulse was slow (52) and the axillary temperature was 97.3°. An aperient was given, but it was vomited and produced no action of the bowels. On the sixteenth day the icteric tint involved the whole skin and the discolouration of the conjunctivæ was more marked. Vomiting had become more frequent and the intolerance of the stomach was absolute, all liquids being rejected. The hepatic and splenic regions were very painful, with a maximum in the region of the gall-bladder, which organ appeared to be enlarged. The temperature and pulse remained the same. An injection of 1000 grams of saline solution was ordered in order to provoke diuresis, as the kidneys had ceased to act since the previous day. In the evening the general condition seemed to have improved. Vomiting had occurred only once during the day. Eighty grams of brownish-red urine, containing 1 gram of albumin per litre and abundance of biliary pigments, had been passed. The patient continued to be very prostrate and spoke of his approaching death. In the night the vomiting recurred and was uncontrollable. At first the vomit was black, then it gradually became sanguineous. There was also constipation. On the seventeenth day the hæmatemesis was incessant and the

patient lost consciousness. The pulse rose to 120 and the temperature to 101.5° and the jaundice increased in depth. Death occurred on this day.

At the necropsy all the tissues had an icteric tinge. The liver did not appear to be enlarged, but it was much congested; on section it looked like a "cardiac liver." Some lobules seemed to be in a state of incipient degeneration. The gall-bladder was voluminous and œdematous. This œdema extended as far as the beginning of the common bile-duct, where an enlarged gland pressed on the latter and appeared mechanically to produce the œdema of the gall-bladder and the icterus. The bile in the gall-bladder was brownish, thick, and very viscid. The stomach contained black fluid; its mucous membrane was spotted with fine ecchymoses which extended as far as the first part of the duodenum. The pancreas was greatly enlarged, œdematous, and congested. It weighed 190 grams and was of a reddish-gray colour. All the region around the pancreas, the duodenum, and the hilum of the liver contained a large number of swollen lymphatic glands. The spleen was enlarged and weighed 1200 grams. The kidneys were a little congested and the capsules were adherent in places. Microscopic examination of the liver showed proliferation of the connective tissue surrounding the biliary canaliculi and a number of nodules composed of embryonic cells. The spleen also contained nodules of embryonic cells and its capsule and trabeculæ were thickened. In the kidneys lesions were limited to the convoluted tubes, the cells of which showed signs of granulo-fatty degeneration and the lumen of which was filled with epithelial débris. The cells and acini of the pancreas were abnormally large, but the islands of Langerhans were diminished, being compressed by the turgescent tubes. The nuclei of the pancreatic cells stained badly and many of them were vesicular.

In this instance the delayed onset of the pancreatic symptoms is remarkable, for they did not occur until the fifteenth day, whereas in most instances they appear to occur about the third or fourth of the illness. In addition to the epigastric pain, which was the principal symp-

tom of the pancreatitis, the gall-bladder was tender and the spleen was tender and enlarged. There was also grave icterus with hæmatemesis, prostration, and subnormal temperature.

An outbreak of epidemic parotitis, accompanied in four cases by symptoms suggestive of metastatic pancreatitis, has been described by Dr. Edgecombe, of Harrogate. The urines from two cases in this epidemic were examined by one of us. In the first no striking abnormality was found and the "pancreatic" reaction was negative. We are informed by Dr. Edgecombe that it was a simple case of uncomplicated parotitis. In the second the urine was acid in reaction, specific gravity 1.030, no albumin, no sugar, a well-marked reaction for acetone and for diacetic acid was obtained, there was a fair amount of indican, a slight pathological excess of urobilin was present, but no bile-pigment was detected, the "pancreatic" reaction (by the improved or C-method) showed many fine crystals, soluble in 33 per cent. sulphuric acid in ten to fifteen seconds. The history of this case, as supplied to us by Dr. Edgecombe, is as follows: April 22d a moderate amount of parotid swelling, with no constitutional disturbance; April 25th the patient was delirious; April 27th there was severe epigastric pain with vomiting, a temperature of 100° F., and a pulse of 96; April 28th the vomiting continued, tenderness and swelling in the epigastrium were detected; April 29th vomiting less, but still pain and swelling in the epigastrium, temperature 102° F., pulse 105; April 30th pain in the epigastrium disappeared, but still slight swelling and tenderness, temperature and pulse normal. It will be noticed that in these two cases the results of the "pancreatic" reaction coincided with the clinical symptoms and course of the disease.

Among the blood infections have to be mentioned "pyæmia," which presents no special peculiarity in the pancreas, and "syphilis," which may affect the pancreas

either as a tertiary affection in the shape of gumma or as a congenital affection, as first described by Birch-Hirschfeld. It produces an interstitial pancreatitis of the interlobular type and the islands of Langerhans are unaffected.

That the spread of ulceration inwards from the stomach may produce an indurative pancreatitis, or even suppuration in the pancreas, can be readily understood, for the ulcer must be constantly bathed with septic matter and the eroding action, when once it has passed through the stomach wall, may assume great activity. The effect of the spread of ulceration is also well exemplified by the case (described later) of pancreatic abscess apparently due to gastric ulcer bursting into the stomach and setting up acute gastritis, for which gastro-enterostomy was performed with a good result.

Whether alcohol can act directly in producing cirrhosis is a matter of great doubt, the probability being that it sets up a gastro-intestinal catarrh which by extension gives rise to the chronic infective process, or another explanation may be in the fact that alcohol causes vascular degeneration, a well-recognised cause of chronic interstitial pancreatitis.

With regard to cirrhosis, the most chronic form of inflammation of the pancreas, which is, though slow in its progress, almost necessarily fatal from diabetes, the cause is probably a long-continued catarrh setting up interlobular and interacinar pancreatitis, which is originally due to infection.

Vascular degeneration is ascribed as a cause of chronic pancreatitis in old or in prematurely aged persons.

CATARRH OF THE PANCREAS

From the foregoing remarks on the etiology of inflammation of the pancreas it will be seen that catarrh of the pancreas is a disease as well worthy of recognition as is

catarrhal jaundice, which in the same way has until recently been thought to be always dependent on catarrh of the bile-ducts. It is held that biliary catarrh is known to exist, as it can be so readily recognised by enlargement of the liver and jaundice, but that catarrhal pancreatitis is beyond recognition. We hope to be able to prove that these views regarding diagnosis will need revising, for catarrh of the pancreas can also be usually verified by digestive and metabolic signs, and by swelling of the gland, which can, in some cases, be recognised by palpation through the abdominal wall, but in others only by manipulation of the pancreas through the opened abdomen. Just as catarrh of the bile-ducts may, and usually does, pass off if the cause be removed, so may pancreatic catarrh entirely clear up under appropriate treatment. Should the cause continue, the catarrh will become chronic and an interstitial pancreatitis ensue which may end in cirrhosis or atrophy of the gland—a condition which probably always has a fatal termination from diabetes.

It will be seen that chronic interstitial pancreatitis is in many cases simply a sequence of pancreatic catarrh, and as the latter is curable by appropriate treatment, and the former, when well advanced, is only capable of relief and probably not of complete cure, it is of the utmost importance that we should recognise catarrh of the pancreatic ducts at an early stage, and if in a short time it fails to yield to medical treatment, that we should perform an exploratory operation with a view to remove the cause, whether that be gall-stones or some other removable condition; but if the cause be not discovered, or if when found it proves to be incapable of removal, then drainage of the bile-ducts, either by cholecystenterostomy or cholecystotomy, will nearly always afford relief: (1) by removing the infected bile and thus ridding the system of poison which tends to deteriorate the blood; and (2) by removing the pressure of pent-up bile from the pan-

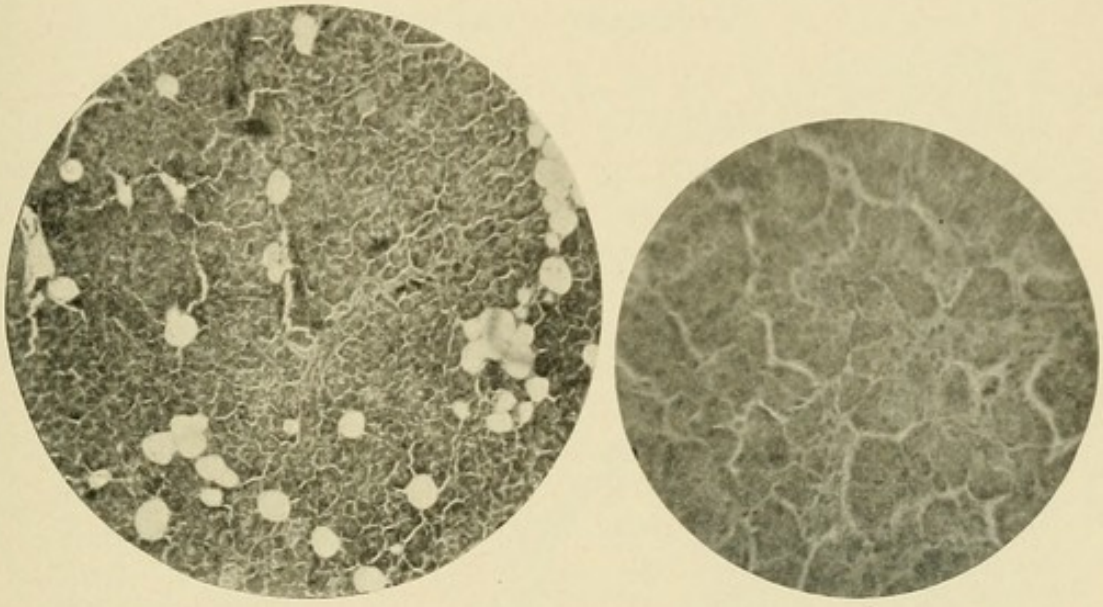
creas, thus relieving tension. Still another beneficial effect will result in some cases where the obstruction is at the papilla, for the pancreatic ducts will then also be drained indirectly through the bile-ducts. In certain cases a mere manipulation of the gland without drainage has been followed by recovery and apparently by cure. An explanation of this result may possibly be that an obstruction in the shape of concretions or adhesions may have been inadvertently removed during the manipulation; but in one case thus treated without drainage glycosuria has subsequently developed, which possibly might have been prevented by draining the ducts in the first instance. An example of the beneficial effects produced by draining the ducts in catarrhal pancreatitis is afforded by the following case:

A patient, aged thirty-eight, after being subject to indigestion for years had biliary colic in July, 1899, and passed gall-stones, which were found in the motions. Subsequently the attacks of pain were frequent and severe, necessitating the use of morphia. They were usually accompanied by icterus, which, though slight, probably never quite disappeared. When seen on November, 1903, he had lost flesh and was prevented from carrying on his professional duties. The metabolic and digestive signs of pancreatic catarrh were well marked. At the operation on November 23, 1903, no gall-stones were found, though the gall-bladder was thickened and adherent to contiguous organs. The pancreas was firmer than usual, though not very much swollen. Cholecystotomy led to recovery, though the drainage of the bile-ducts had to be continued for three months. The patient is now well.

In this case the pancreatic catarrh had evidently been set up by the passage of gall-stones through the common duct. The pancreatitis had, however, persisted, and was not only keeping up painful symptoms, but leading to obstruction of the bile-ducts and to interference with nutrition. This case would formerly have been called

catarrhal jaundice, whereas it was really due to catarrhal pancreatitis, as proved by the digestive and metabolic signs and later by operation.

Just as post-mortem evidence is not easy to obtain in simple catarrh of the liver, so it is reasonable to anticipate that pathologists will rarely find gross lesions of the pancreas, even if opportunity for a post-mortem examination occurs, in cases of catarrhal pancreatitis. The micro-photographs in Fig. 121 are from a case of



a *b*

Fig. 121.—*a*, Catarrh of the pancreas during incipient stage of interstitial pancreatitis (× 30); *b*, a portion of the same more highly magnified, showing the round-celled infiltration (× 190).

early interstitial pancreatitis where death occurred in an aged patient twelve hours after operation, apparently from a cerebral attack that came on during anæsthesia. A gall-stone was impacted in the common duct and pressed on the pancreatic duct, the pancreas being found swollen at the time of operation. There was a well-marked pancreatic urinary reaction before operation. At the necropsy no gross lesion of the pancreas could be seen, but microscopically there were small-celled infiltration,

congested vessels, in fact, an incipient interstitial pancreatitis, and it is probable that careful investigation would demonstrate similar microscopic lesions in cases where no gross changes are manifest.

It is not necessary to consider separately the symptomatology of acute and chronic catarrh of the pancreas, as the symptoms and signs, though less in degree, are practically the same as those of chronic pancreatitis, under which subject they will be fully dealt with.

SUPPURATIVE CATARRH

This disease bears the same relation to simple pancreatic catarrh that simple catarrhal jaundice does to suppurative cholangitis and, like the latter, it is an extremely serious and frequently a fatal disease. In all the cases we have seen gallstones have been the cause, but why some patients should have simple catarrh ending in chronic interstitial pancreatitis and others should at once develop an acute suppuration of the pancreatic duct it is difficult to say, unless one may surmise that in the latter class the infection may be of a more virulent character and the patient's tissues less able to withstand the attack. The disease tends towards death from septi-

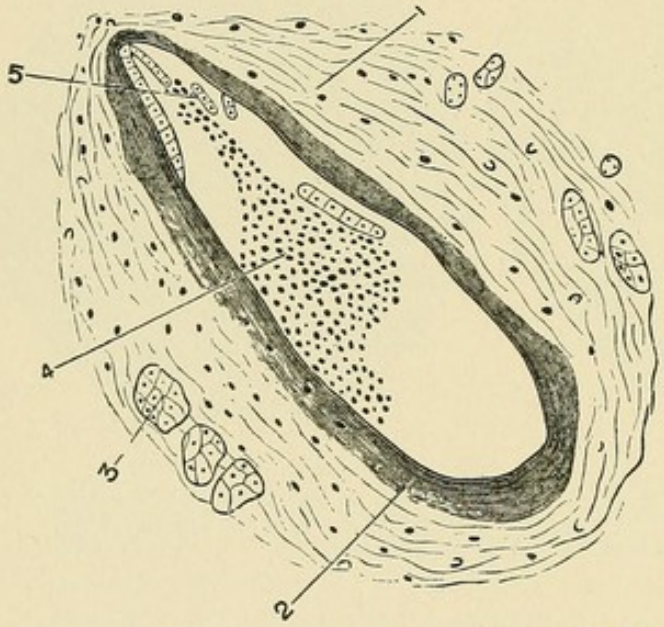


Fig. 122.—Camera lucida drawing of suppurative catarrh of the pancreatic ducts: 1, Exudation and cells, 2, duct; 3, acini; 4, pus; 5, detached epithelium (A. J. Chalmers, Journ. of Ceylon Branch of Brit. Med. Assoc., vi, part 2, 1904).

cæmia, or if the process be less acute, or the vital powers more resistant, it may possibly end in a localised abscess. Suppurative catarrh of the pancreatic ducts is generally, if not always, combined with suppurative cholangitis. The following four cases illustrate the serious nature of the disease, but show that it is not necessarily hopeless if treated early.

If the suppurative catarrh be diffuse and involve the ducts throughout the liver and pancreas, the associated septicæmia is very serious, as the following case, seen with Dr. Hector Mackenzie, proves:

Mr. W———, aged sixty-five years, seen on January 4, 1904. He had had attacks of gall-stones seven years before and two seizures during the last two years, both of which were followed by jaundice. His present illness started on November 23d with severe pain, followed by jaundice. On December 20th a very severe attack of colic was followed by more intense jaundice and enlargement of the liver with irregular temperature and ague-like attacks. The patient had had albuminuria for seven or eight years. On examination there was tenderness above and to the right of the umbilicus and he had severe pain. A specimen of the urine was examined, and found to give a marked pancreatic reaction, and to contain calcium oxalate crystals. On opening the abdomen on January 7th, firm adhesions were encountered, and on detaching the omentum, phlegmonous cholecystitis was discovered, with gangrene of the fundus of the gall-bladder; pus escaped freely, but the peritoneal cavity was saved from being soiled by means of sponge packing. The common duct was enormously dilated and embraced by the swollen pancreas, but no gall-stones could be felt. On opening the common duct a large quantity of pus and bile escaped. By means of the scoop passed into the common duct and the fingers passed behind the pancreas a number of gall-stones were extracted, but a hardness could be felt at the papilla which could not be removed. On laying this open after incising the duodenum, a gall-stone was removed from the ampulla of Vater, and pus was immediately seen to flow from the duct of Wirsung. The duo-

denum was then closed, the gangrenous upper part of the gall-bladder was removed, and the common duct and gall-bladder were drained. The patient bore the operation well, and from that time onwards had no more fever, but for the fortnight during which he lived his temperature was persistently subnormal. He had no peritoneal symptoms and the bowels were moved freely from the second day onwards. Calcium chloride had been given before operation, and at the operation he lost no blood. None was given subsequently to operation, as the rectum was intolerant of injections, and on the eighth day there was rather free oozing of blood from the drainage track, which had to be treated by gauze packing, after which the calcium chloride was resumed, and no more bleeding occurred. On the eleventh day the patient became somnolent and declined to take food. From this time he got gradually weaker, and died comatose on the fourteenth day in a condition almost resembling that associated with acute atrophy of the liver.

If the suppurative catarrh takes on a very acute form, the development of abscess in the liver and pancreas may occur, and the condition become one of pyæmia, when the chance of recovery will be very remote, as in the following case:

The patient, a woman, aged sixty-five years, seen with Sir William Broadbent and Dr. Bousfield, was suffering from deep jaundice, suppurative cholangitis, pancreatitis, and parotitis of pyæmic origin; rigors with a temperature of 105° occurring daily, or even twice a day, the acute symptoms having come on within a fortnight, though there had been a history of gall-stones for years. The common and hepatic ducts were filled with gall-stones, which were removed through an incision in the common duct, and a large quantity of extremely offensive pus and bile was evacuated. At the same time the right parotid gland (the seat of inflammation) was incised. The bile was examined bacteriologically, and found to contain the bacillus coli in large numbers; next in numbers were streptococci and another rather fine bacillus, which appeared to grow anaërobically only, and there was a fine spore-

bearing organism, probably the bacillus putrificus coli. The urine gave a well-marked pancreatic reaction. The patient, who had also heart disease and albuminuria, appeared to be doing well for twenty-four hours, when she died suddenly, apparently from cardiac thrombosis.

If the suppurative catarrh assumes a subacute form, it may end in a simple pancreatic abscess, which can be successfully evacuated, as in the following cases:

Mrs. P., aged sixty-one, gave the history of having been subject to biliary colic for three or four years, though there had been no jaundice till two and a half years ago, since which time the attacks of pain had always been accompanied by rigors and by deepening of the jaundice. Within a short time of being first seen, the symptoms had become aggravated, and the loss of flesh had become extreme. The patient was so ill that the question of cancer of the pancreas was raised, but the pancreatic reaction in the urine and a chemical examination of the fæces definitely pointed to inflammation and not to growth. At the operation the pancreatic portion of the common duct was packed with large gall-stones and the head of the pancreas was markedly swollen. On passing the scoop through the opening in the common duct, a stone the size of a cherry was extracted from the pancreatic portion of the duct, it being covered with offensive pus. This had apparently lodged in a cavity in the head of the pancreas. A profuse discharge of bile and offensive pancreatic fluid with pus continued to pass for a week, after which the discharge became gradually less. She made a good recovery, and was well two years later.

In general subacute pancreatitis, starting as suppurative catarrh with the formation of a localized abscess, the pancreas may be so damaged that after the abscess has been cured by drainage, the extensive interstitial pancreatitis may ultimately lead to the death of the patient at a longer or shorter interval, as in the following cases:

Mr. H., aged forty, had suffered from continuous fever, with exacerbations associated with rigors, that recurred

almost daily. He gave the history of failing health for nine months, and of having had gall-stone attacks much longer, but the acute symptoms associated with jaundice had only been present for a fortnight. The pancreatic reaction was found in the urine. At the operation, on October 11, 1900, he was far too ill to bear a prolonged search, and as the adhesions were very firm, it was felt desirable only to drain the bile-ducts through the gall-bladder, though a marked swelling of the pancreas made it appear probable that an abscess might be present. A large quantity of muco-pus drained from the gall-bladder and a number of gall-stones were removed. The abscess of the pancreas discharged subsequently through the drainage-tube, after which the pancreatic swelling subsided. The patient made a slow though steady recovery, and returned home early in December. Though he was able to get out and to take food, he never fully regained his strength, and died in February of the following year. At the necropsy the pancreas was found to be much enlarged and to be the seat of interstitial pancreatitis. The cavity where the abscess had been was occupied by a little pulpy material, but no further collection of pus was formed, nor were any gall-stones discovered in the bile-ducts. A microscopic examination of the pancreas showed advanced interstitial pancreatitis.

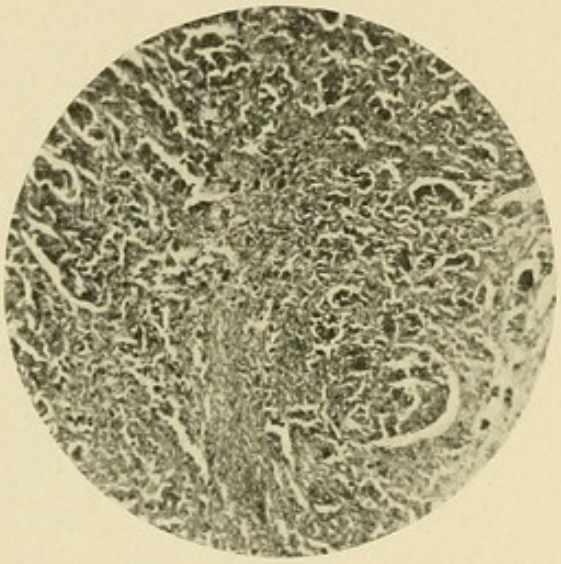


Fig. 123.—Microphotograph of the pancreas from a case of chronic suppurative pancreatitis (× 40).

The preceding cases are most instructive in that they illustrate one of the dangers of cholelithiasis, which might be avoided by appropriate treatment at an earlier stage, for the removal of gall-stones before the onset of deep

jaundice and infection of the bile and pancreatic ducts is with due care and in skilful hands almost devoid of danger. So far as we know, these conditions were first described in the Hunterian Lectures for 1904 as separate and distinct diseases. The reasons given and the cases related show a justification for separating catarrhal inflammation about to be described. Simple catarrh of the pancreas can be treated most successfully if taken in time, but, as will have been noticed, suppurative catarrhal pancreatitis is quite as serious as acute phlegmonous pancreatitis, and unless treated surgically must be almost necessarily fatal.

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CHAPTER XV

ACUTE PANCREATITIS AND SUBACUTE PANCREATITIS

ACUTE PANCREATITIS

Symptoms.—Acute pancreatitis is usually ushered in by a sudden pain in the superior abdominal region, accompanied by faintness or collapse, and followed, sooner or later, by vomiting. There is usually some epigastric swelling with tenderness from the first, and if the warm flat hand be placed over the epigastrium, and retained there without movement for a time, it will be found that the swelling is diffuse and not simply dependent on a distended stomach or colon, though later, when peritonitis is established, the hollow viscera become inflated. It is almost constantly accompanied by constipation, so that it is quite usual for these cases to be mistaken at first for intestinal obstruction. The obstruction, however, is not absolute, flatus passes, and a large enema may secure an evacuation; if the patient survives for several days diarrhœa may supervene. The pain may be so severe as to produce syncope or collapse, and though the pain does not quite pass away, it has a tendency to be paroxysmal and to be increased by movement; it is associated with well-marked tenderness just above the umbilicus and between it and the ensiform cartilage. The pain is soon folowed by distension in the superior abdominal region, which may become general, and usually does so in the later stages, and by vomiting, first of food, then of bile, and soon of black, altered blood. The vomiting may be severe and each attack of sickness aggravates the pain. Rarely vomiting may not be a prominent symptom.

Slight jaundice from associated catarrh of the bile-ducts and pressure is usually present and deepens the longer the patient survives. As the impaction of a gall-stone in the ampulla of Vater is probably one of the most frequent causes, the jaundice may become intense, from a complete stoppage of the passage of bile into the duodenum. The aspect is anxious and the face is pinched, resembling the facies of peritonitis, which, in fact, is usually present. The pulse, which is rapid and small, is a better guide than the temperature, which may be normal, subnormal, irregular, or high. In the ultra-acute cases the temperature is usually subnormal, but in the cases that survive for several days the temperature becomes irregular and may be excessive. Delirium comes on in the later stages. The distension and tenderness may prevent an exact examination of the pancreas, which would otherwise be found enlarged. Death usually supervenes from the second to the fifth day from collapse, probably due to absorption of virulent matter, though in the less acute cases life may be more prolonged and recovery may possibly occur, as in cases related below, proved by laparotomy and the discovery of extensive fat necrosis, and by others reported elsewhere. Acute pancreatitis thus takes on the form of acute peritonitis starting in the superior abdominal region. If life be prolonged, the condition may become one of subacute pancreatitis, the onset in such a case being usually less grave, though often equally sudden. It is even possible for the trouble to resolve, apparently completely, and then for a relapse to occur, this sequence being repeated on several occasions.

The preceding description refers to acute pancreatitis generally and applies to the hæmorrhagic, gangrenous, or suppurative varieties, which are phases of the same infective conditions, though the morbid appearances differ so much. In gangrenous pancreatitis the organ is dry and dark or even black, and there can be little doubt, as

Opie has remarked, that this condition represents a late stage of the hæmorrhagic form. What has been previously said concerning pancreatic hæmorrhage will show that neither clinicians nor pathologists are agreed on this subject, some believing that inflammation precedes the hæmorrhage,—among these being Fitz, who designates the disease "hæmorrhagic pancreatitis,"—others holding that the hæmorrhage precedes inflammation, which is, in fact, caused by bacterial infection of the hæmorrhagic effusion. It is probable that both views may be correct in different cases, for although a primary pancreatitis may be accompanied by hæmorrhage, yet this origin is not the only one, and there are many cases in which hæmorrhage precedes and, in fact, is the cause of, inflammation; first, owing to the great tendency of the gland to disruption because of its soft structure when hæmorrhage does occur; secondly, owing to the setting free of the pancreatic secretion which decomposes and digests the damaged tissues; thirdly, owing to the communication of the gland with the intestine, rendering the access of putrefactive organisms likely; and, fourthly, owing to the great tendency of the damaged gland and the effusion to become decomposed as soon as organisms gain access. From its proximity to the peritoneum, acute peritonitis rapidly follows acute pancreatitis. These two varieties of hæmorrhagic pancreatitis may at times be clinically differentiated, the ultra-acute, with a violent and sudden onset, accompanied by collapse and ending fatally with extreme rapidity, being for the most part the ones where the hæmorrhage precedes the inflammation, and the somewhat less though still acute cases, where the onset is more gradual, where the symptoms are not ushered in by collapse, and where resolution and relapse are liable to occur, being the ones where the inflammation precedes the hæmorrhage. The varieties in which the inflammation precedes the hæmorrhage may in the severer forms

Fig. 124.—Pancreas and adjacent tissues from a case of acute hemorrhagic pancreatitis with fat necrosis (St. Bartholomew's Hosp. Museum).

approach the subacute varieties of pancreatitis. These views simplify the subject and place the disease of hæmorrhagic pancreatitis in a line with other well-known inflammations. The coloured plate (Fig. 124) shows a striking specimen of acute hæmorrhagic pancreatitis with fat necrosis, preserved by the Keiserling process, in St. Bartholomew's Hospital Museum.

The specimen represented in Fig. 125, copied from Nothnagel, is in the Warren Anatomical Museum of Harvard Medical School. It exemplifies a case of true

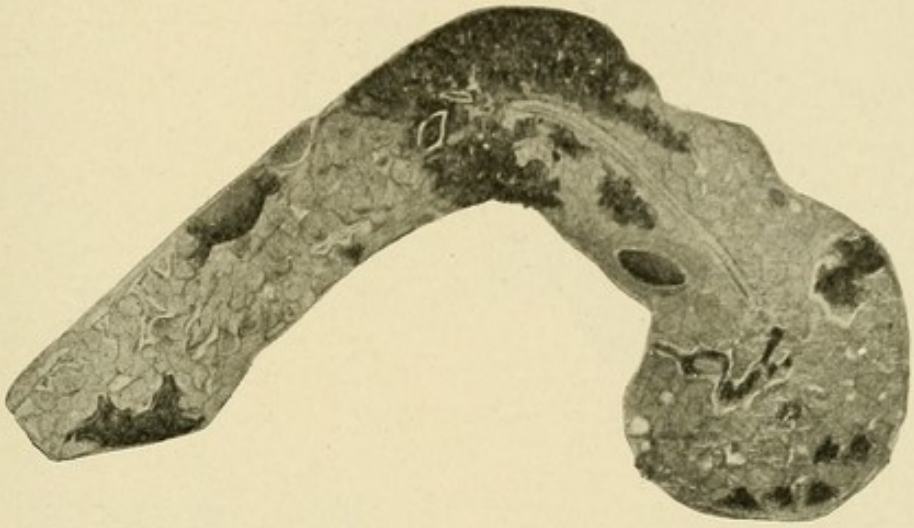

Fig. 125.—Acute hæmorrhagic pancreatitis (Oser).

hæmorrhagic pancreatitis, of four days' duration, in which the inflammation was the cause of the hæmorrhage.

A well-marked example of hæmorrhagic pancreatitis from the museum of the Leeds Medical School, which was under the care of Mr. B. G. A. Moynihan and was dependent on gall-stones, is seen in Fig. 126.

A specimen in St. George's Hospital Museum (204 A) is a good example of hæmorrhagic or necrotising pancreatitis (Fig. 127). The case was reported in the "Lancet" of October 19, 1901, p. 1041.

Etiology.—In many cases of acute pancreatitis the etiology is obscure, for although the disease is capable of

being produced artificially by injection of bile, bile salts, and other substances into the main pancreatic duct, yet

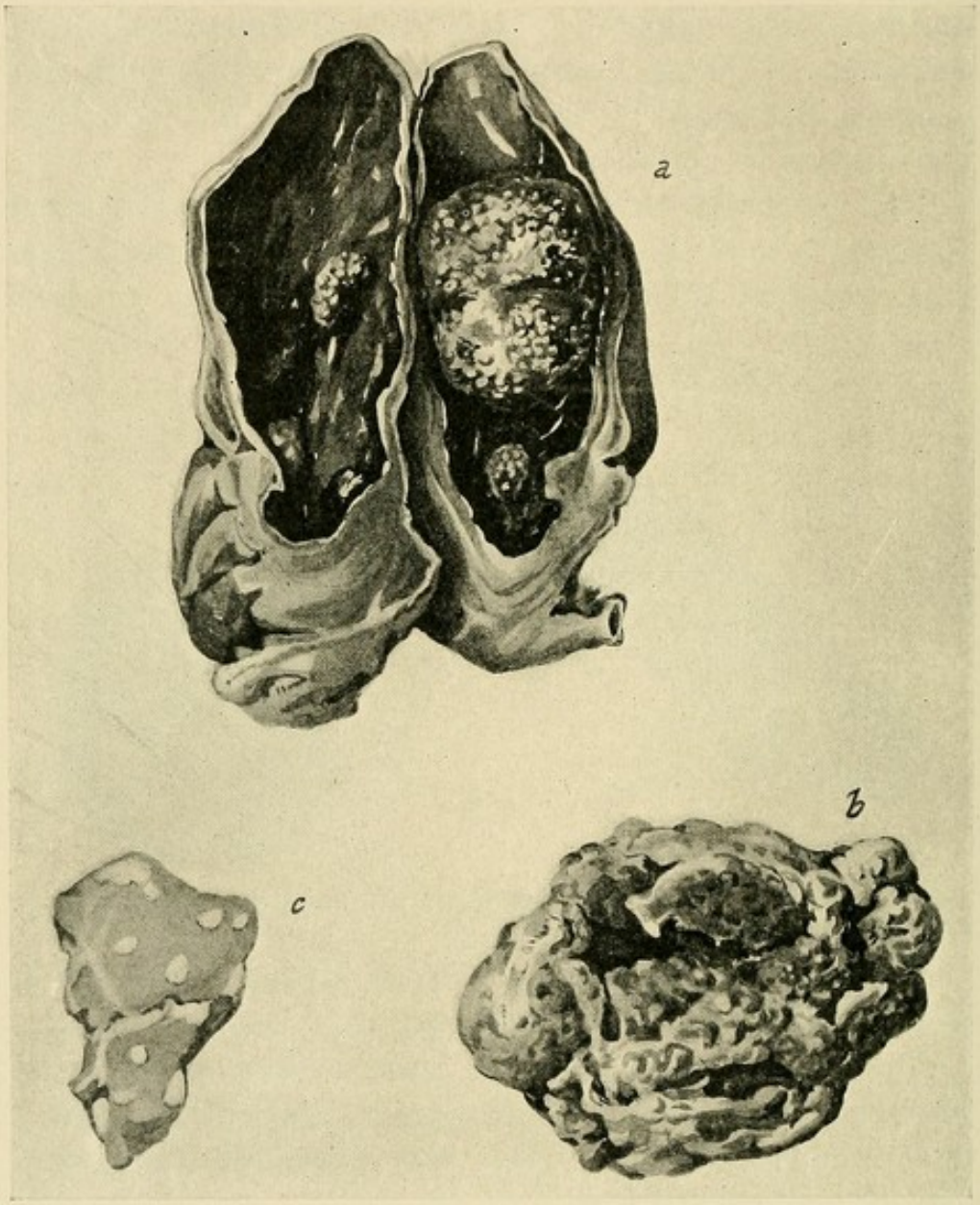

Fig. 126.—Specimens from a case of acute pancreatitis (Leeds Museum, E E 200): *a*, Gall-bladder containing stone; *b*, slough of the pancreas; *c*, piece of omental fat, showing fat necrosis.

in only a few cases has it been produced in a similar way by diseases in the human subject.

In some cases septic influences have been causative and

in others blood disorders, but in a considerable number of reported cases gall-stones either directly or indirectly have been instrumental in setting up the disease.

If a small gall-stone happens to descend into an unusually large diverticulum of Vater and to lodge there, it will make a through channel from the common bile-duct into the pancreatic duct, and so set up acute pancreatitis, the infected bile being forced direct into the pancreatic duct, as in Dr. Halsted's case, reported in Opie's work on the pancreas.

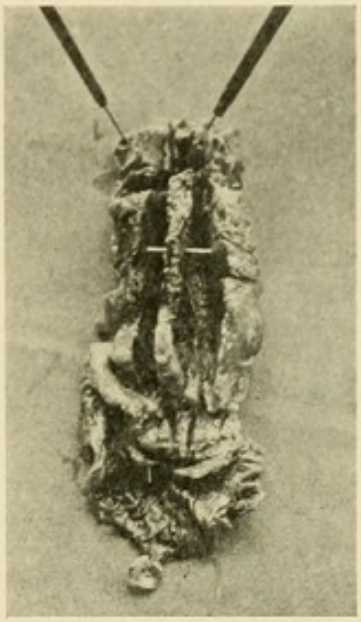

Fig. 127.—Acute hæmorrhagic pancreatitis and necrosis of the pancreas (St. George's Hosp. Museum, 204 A).

"L. F., male, aged forty-seven years, was admitted to the Johns Hopkins Hospital complaining of abdominal pain and fever. He had suffered with somewhat frequent attacks of indigestion, characterised by pain after eating, distension, and rarely nausea and vomiting, but otherwise had enjoyed good health. Six months before his present illness he had had an attack of jaundice, lasting about three weeks, and accompanied by abdominal pain. The present illness began eighteen days before admission, when he was suddenly seized with violent nausea and vomiting, accompanied by intense cramp-like pain in the abdomen. The vomiting continued during the first night, and had since only occasionally recurred. The abdominal pain, which was not localised, remained severe during four or five days, and at times there were symptoms of collapse. The abdomen was distended and the bowels were constipated until the fifth day, when, with the aid of a purgative, movement occurred. The stool was normal in colour. On the third day elevation of temperature to 101.5° F. was noted. About the seventh day tenderness and slight swelling were noticed in the right hypochon-

drium. Since this time the patient had an irregular temperature (100° to 103° F.), with several chills. After the first few days the abdominal pain and tenderness were not severe, but the distension of the abdomen gradually increased. Jaundice was not noticed.

"*Physical examination:* The conjunctivæ have a slight yellow cast. On inspection of the abdomen a distinct prominence is found to occupy the right hypochondriac and right half of the epigastric region, extending into the upper half of the umbilical region. Its lower margin, which descends on inspiration, is felt in the middle line at the level of the umbilicus. Its right border cannot be sharply defined, but in the median line the fingers can be pressed in above it. Over the resistant mass there is dull tympany. The leucocytes number 1800. The urine is clear, its reaction is acid, and specific gravity 1.017. There is no reduction of Fehling's solution. A trace of albumin is present. On the second day after admission a stool passed was of a golden yellow colour. On the third day the leucocytes numbered 19,500, and the temperature varied from 99.2° to 101.8° F. During the night the patient was irrational at times. The temperature rose gradually, reaching a maximum of 104° F. A liquid stool of ochre-yellow colour was passed. The urine had a specific gravity of 1.020 and no reaction for sugar was obtained. A diagnosis of suppurative pancreatitis was made and an operation for its relief was performed under cocaine anæsthesia. A linear longitudinal incision was made below the costal margin within the right mammillary line. After incising the great omentum between the stomach and transverse colon, an abscess cavity was entered. Grumous, purulent fluid, containing necrotic particles, was evacuated. A rubber drainage-tube, packed about with gauze, was inserted into the wound. After operation the pulse remained weak, and death followed at the end of about four hours. The duration of the fatal illness was twenty-one days.

"*Autopsy:* Performed three hours after death. The body is that of a large-framed, muscular man, with abundant subcutaneous fat. The omentum, which contains a large quantity of fat, is thickly studded with conspicuous opaque white areas, usually round, and about 3 mm.

in diameter. Similar opaque white areas are present in the fat of the mesentery, in the subperitoneal fat of the abdominal wall, over the bladder, over the kidneys, and about the colon. The drainage-tube inserted into the abdominal wound passes through a small incision in the great omentum and enters an immense abscess cavity; the foramen of Winslow is closed. The walls of the cavity are very irregular and ragged, and have a necrotic appearance, in general opaque and grey, occasionally black. The blackish-grey appearance extends only a short distance below the surface, and where the wall is formed of fat gives place to numerous foci of opaque white colour. The retroperitoneal fat in front of the left kidney and psoas muscle has been eroded, and an extension of the cavity passes behind the jejunum near its junction with the duodenum. To the left of the descending part of the duodenum, occupying the position of the pancreas, and projecting forward into the abscess cavity, is a great mass of black material, necrotic in appearance, extending to the left as far as the spleen. The material is reddish-brown on section, somewhat spongy in texture, soft, dry, and friable. The cavity contains at least 500 c.c. of fluid, reddish-grey material, in which are fat droplets and black necrotic particles. The liver is flaccid in consistence. The bile-ducts are slightly dilated, and contain thin, yellow bile. The gall-bladder is bound by numerous adhesions to the duodenum and stomach. Its walls are thickened and it is much distended, containing viscid yellow bile and more than one hundred brown, faceted calculi, varying in diameter from 0.5 to 1 cm. The hepatic, cystic, and common ducts are much dilated. On opening the duodenum a stone is felt below the mucous membrane, situated in the common bile-duct near its termination. It is 7 mm. in diameter and resembles those present in the gall-bladder. The pancreatic duct unites with the common bile-duct at a point 7 mm. from the duodenal orifice. The pancreatic duct is not distended. The pancreas occupies the posterior wall of the abscess cavity of the lesser peritoneum, and is covered by the mass of reddish-brown, friable material, changed coagulated blood-clot, above described. The organ is of large size, and the glandular tissue is in great part firm,

yellowish-white, and well-preserved. The interstitial tissue has a dull reddish, in places hæmorrhagic appearance, and contains conspicuous opaque yellow areas of irregular shape. Where the anterior surface of the head and body is in contact with the overlying material there is a superficial zone of soft, greyish, necrotic appearance. The other organs present no noteworthy alteration.

"*Histological examination:* The interstitial tissue of the pancreas is much increased and wide bands of fibrous tissue separate groups of lobules. Numerous irregularly shaped cells filled with brownish-yellow pigment granules, which give the prussian-blue reaction for iron, afford evidence of former hæmorrhage. In a few places well-preserved red corpuscles are scattered in the tissue. Foci of necrotic fat are present. Many acini are widely dilated; their cells are flat and the lumen is much distended, containing products of secretion and occasionally one or more polynuclear leucocytes. In an area corresponding to the superficial zone of necrotic appearance before mentioned, nuclei no longer stain, and the architecture of the glandular tissue is only obscurely distinguished. A thick band of newly formed fibrous tissue containing an occasional acinus or duct separates the necrotic parenchyma from that which is still intact. The mass covering the pancreas is found to consist of altered blood; upon and immediately below its surface are numerous polynuclear leucocytes.

"*Bacteriological examination:* Cultures from the blood contained in the heart, from the lungs, and from the liver, were found to contain the bacillus coli communis. A plate culture from the material covering the pancreas, and forming part of the abscess wall, contained the bacillus coli communis, the bacillus lactis aërogenes, and the bacillus proteus vulgaris.

"*Anatomical diagnosis:* Cholelithiasis; calculus lodged in the common bile-duct near its orifice; slight jaundice. Old hæmorrhage within and about the pancreas, with localised necrosis and chronic inflammation; necrosis of the fat of the pancreas, greater and lesser omentum, mesentery, and subperitoneal fat of the abdominal wall; peri-pancreatic abscess limited by the lesser peritoneal cavity. Laparotomy wound."

A somewhat similar case has more recently been reported by Bunting in the "Johns Hopkins Hospital Bulletin."

"A well-nourished man, aged fifty-one, was subject to attacks of epigastric pain with some constipation, which were usually easily relieved. He was seized with intense epigastric pain, became collapsed, and showed considerable abdominal distension. Intestinal obstruction was diagnosed and laparotomy was performed. Some peritoneal adhesions were freed and the wound was closed. There was no fat necrosis to attract attention to the pancreas. Death occurred on the following morning. At the autopsy both chronic interstitial and acute hæmorrhagic pancreatitis were found. The pancreas was large, swollen, and mottled with red areas of hæmorrhage and opaque areas of fat necrosis. The gall-bladder was distended with bile and the bile-ducts were dilated and firm to the touch, showing that there was obstruction to the flow of bile. On gentle pressure bile did not escape from the papilla, but on increased pressure there was a sudden escape of bile, carrying before it a small yellowish-white mass, which was unfortunately lost. In the bile-ducts a stone about 2 mm. in diameter was found in the apex of the ampulla of Vater, close to the orifice. In the gall-bladder and cystic duct were about 400 soft, light-coloured cholesterin stones, varying from 0.5 to 6 mm. in diameter. There was therefore little doubt that the escaped mass was a stone. The anatomical relations of the ampulla and ducts were such that the obstruction set in progress the mechanism described by Opie, and resulted in the injection of bile into the pancreatic duct. This duct joined the common bile-duct 11 mm. from the tip of the papilla and was dilated and bile-stained for 4 cm. from its orifice. The common duct was dilated and somewhat hypertrophied. This, in connection with the induration of the pancreas, seemed to indicate that the previous attacks of pain were due to the passage of gall-stones, some of which might have been large enough to block the pancreatic duct in transit and cause the chronic interstitial pancreatitis."

But the anatomical conditions just mentioned, though evidently potent, are certainly not necessary for the production of acute pancreatitis. Any gall-stone or stones impacted in the pancreatic portion of the duct, or even filling the ampulla of Vater, may produce acute pancreatitis, as in a case under the care of Dr. Fison, of Salisbury.

"A man, aged thirty-nine, had a sharp attack of diarrhœa on March 27, 1904, having been previously constipated. The next day, about one and one-half hours after dinner, he was seized with severe epigastric pain followed by vomiting. At 5 P. M. he looked anxious and ill, and the abdomen was tense and tympanitic, but there was no jaundice. The vomiting persisted. There was tenderness over the gall-bladder and to a less degree over the stomach, but no enlargement of the liver or any indication of tumour. Temperature, 98°; pulse, 110.

"The next day the temperature was 97° and pulse 120; the vomiting continuing, morphia was given. On the 30th the temperature was 96.8°, the pulse 125, small, weak, and thready, respiration 36. The pain was easier. Urine scanty and dark.

"*Operation* on evening of the 30th, fifty-four hours after first attack of pain. Very extensive fat necrosis found in subcutaneous tissues and in omentum, mesentery, etc. Large quantity of brown inoffensive fluid in peritoneum. Incision made into tissues around pancreas through mesocolon. Gall-bladder drained through another incision, many gall-stones removed. Free drainage of abdomen. After recovery from anæsthetic the vomiting persisted, and the pulse remained absent from the wrist up to death, some hours later.

"At post-mortem examination a pint of bloody fluid in peritoneal cavity. Base of mesocolon filled with friable offensive material, blackish-brown in colour, and here and there streaked with pus. Pancreas much swollen and weighed seventeen ounces. Hæmorrhagic infiltration in centre of body and another in tail; consistency very firm, with swelling of lobules. In the cystic duct were three gall-stones, in the common duct four, and in the hepatic duct four. One gall-stone $\frac{3}{8}$ inch in length

completely filled the ampulla of Vater, into which the duct of Wirsung opened one-third of an inch from the papilla. The duct of Wirsung did not contain bile.

"Urine sent for examination by Dr. Cammidge showed crystals soluble in one-half minute by the 'A' reaction, and a few crystals by the 'B' reaction soluble in the same time.

"The following is Dr. R. Salisbury Trevor's report of examination of the pancreas:

"The gland is enlarged in all its diameters, the margins being rounded off and producing as a consequence a sausage-shaped contour. In the head, the middle of the body, and the tail are chocolate-coloured areas, which are fairly sharply differentiated from the surrounding parenchyma in which the normal lobulation is visible. The duct of Wirsung is not bile-stained. The portion of common bile-duct attached to the head of the gland appears to be somewhat dilated. Around the gland, as well as in it, are numerous typical foci of fat necrosis.

"Microscopical examination: Sections have been prepared from the head, body, and tail, in most instances to include the chocolate-coloured areas as well as apparently normal parenchyma. The dark coloured areas are due to necrosis of the parenchyma associated with hæmorrhage, and in the sections from the head and tail are demarcated off from the neighbouring gland acini by well-marked zones of inflammatory small-celled infiltration. In the tail section inflammatory reaction is absent, the necrosed areas merging gradually with the unaffected parenchyma. In the necrosed areas the gland parenchyma is only barely recognisable by a faint alveolar structure, all gland elements having disappeared. The whole of these areas stain badly. In the necrotic portions the smaller blood-vessels are filled with more or less hyaline thrombi. Around the necrotic areas in the head and body is a deposit of old blood-pigment, and the appearances rather suggest that here the lesions are of older date than those in the tail. Inflammation is most marked in sections of the head. The remaining gland parenchyma is badly preserved owing to auto-digestion, and the head appears to show a slight grade of chronic

interstitial pancreatitis of the interlobular type. Throughout the sections the islands of Langerhans are found with difficulty, and, from comparisons with other sections, their number in the tail sections at all events appears to be diminished. Two of the islands of Langerhans found in the tail sections are very large in size. The cells, however, are rather broken up, and into one of them hæmorrhage has occurred. Minute changes are not recognisable owing to bad preservation of the tissue. The epithelium of Wirsung's duct shows distinct signs of a catarrhal change.

"*Summary.*—The condition is one of acute pancreatitis, with hæmorrhage and necrosis (the acute form of hæmorrhagic pancreatitis in Mayo Robson's classification)."

Owing to Dr. Fison's kindness we are able to show photographs of the extensive fat necrosis found in his case (see Figs. 87, 88).

The following is a case of gangrenous pancreatitis due to gall-stones, which recovered after operation:

Mr. S——, aged fifty-eight, had for six years been subject to paroxysmal attacks of acute pain, starting in the right hypochondrium and radiating over the abdomen and through to the right scapula, the attacks being accompanied by vomiting and more or less collapse. On several occasions he had passed small gall-stones.

About ten weeks before being seen by one of us he was seized with an attack which did not, as usual, yield to morphia. The liver became enlarged and tender; there was a great amount of flatulence and acidity and a feeling of discomfort generally. After this seizure he had ague-like attacks and jaundice of varying intensity, and from that time a tumour steadily developed in the epigastric and right hypochondriac regions. He rapidly lost flesh and strength, and when he was taken into a surgical home for operation he was so feeble and emaciated that it was questionable whether he would be strong enough to bear it. Jaundice was well marked, and the tumour in the upper abdomen, which was tense, tender, and fluctuating, was still enlarging. He had had diarrhœa six times a

day for several days before admission, and the motions were bulky and pale and contained fat. The urinary pancreatic reaction was well marked. Just before operation he vomited clear fluid, not containing bile. Operation was performed on April 5, 1902, when a pancreatic cyst was exposed between the stomach and colon, containing four pints of straw-coloured fluid. Inside the cyst was found a mottled black slough with grey patches, $2\frac{1}{2}$ to 3 inches long by $1\frac{1}{4}$ inches broad, and $\frac{1}{2}$ inch thick, evidently pancreas. (See Figs. 128 and 129.) The gall-bladder and ducts contained thirty stones, two the size of walnuts. One of these was found at the junction of the cystic and common duct, and pressing on the latter. The cysts of the pancreas and the gall-bladder were drained by separate tubes, with the stomach and the first part of the duodenum between them. On being put back to bed the patient was quiet, but vomited frequently. He made a steady recovery without any untoward symptoms, and left for home on May 2, 1903. On March 3, 1904, the patient was the picture of health, and had gained $1\frac{1}{2}$ stones in weight. He states that the gall-bladder opening had closed in six weeks and the pancreatic fistula in nine weeks.

Fig. 128.—Slough of the pancreas removed at operation. Recovery (Royal College of Surgeons Museum, 2834 B).

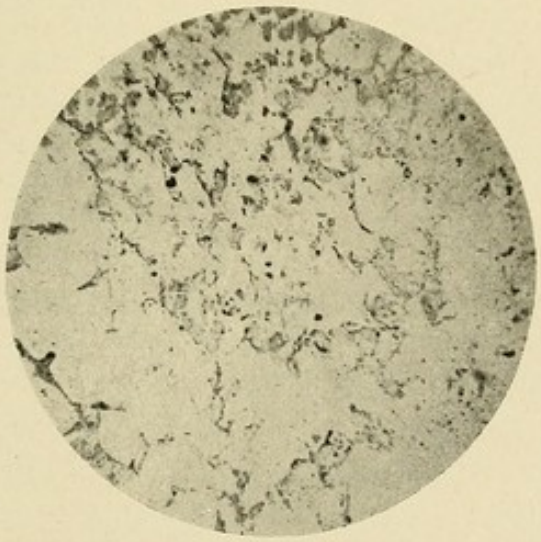

Fig. 129.—Microphotograph of necrosed pancreas shown in Fig. 128 (× 40).

Although gall-stones would appear to be the most frequent cause of acute pancreatitis, yet the following cases operated on by one of us show that other conditions may cause it.

In the case of a young woman suffering from acute suppurative pancreatitis the viscera were found hopelessly matted together and there was extensive fat necrosis all over the abdomen. There was no definite history of gall-stones, nor could any be found at the time of the operation. A subphrenic abscess containing masses of necrosed fat and dark pus was evacuated and drained. This only gave temporary relief to the patient, who succumbed on the third day after operation, apparently from septic absorption.

In another case, a young man, aged twenty-eight, slipped and fell forward against a board projecting from the end of a table at which he was working. The blow was comparatively slight and the man did not fall to the ground. Acute pancreatitis followed on what was probably a mere bruising of the pancreas, followed by slight bleeding into the gland, but the effusion becoming infected, acute hæmorrhagic pancreatitis supervened. An exploration for the cause of the peritonitis resulted in the discovery of a large collection of highly blood-stained fluid in the lesser peritoneal sac, some of which had burst through a small laceration in the omentum into the greater sac of the peritoneum. There was general peritonitis present at the time of operation, and though drainage was freely adopted both from the front and through the loin, the patient did not survive many hours.

In the one case extension of infection from the duodenum was probably the cause; in the other, traumatism; but metastasis from mumps, blood conditions, and infection from various diseases, such as typhoid fever, pyæmia, etc., may be the cause, as in cases reported later.

Diagnosis.—The diagnosis of acute pancreatitis is at first difficult, as the symptoms are only characteristic of peritonitis starting in the upper part of the abdomen.

Fitz's rule is worth bearing in mind: "Acute pancreatitis is to be suspected when a previously healthy person, or sufferer from occasional attacks of indigestion, is suddenly seized with violent pain in the epigastrium, followed by vomiting and collapse, and, in the course of twenty-four hours, by a circumscribed epigastric swelling, tympanitic or resistant, with slight rise of temperature." In case of laparotomy the presence of extensive fat necrosis is almost pathognomonic.

At first the differential diagnosis must be made from intestinal obstruction, perforating duodenal or gastric ulcer, ruptured gall-bladder or bile-ducts, phlegmonous cholecystitis, and gangrenous appendicitis. In considering the difficulty of diagnosing between acute pancreatitis and intestinal obstruction it has to be borne in mind that the two may coexist, as the swollen pancreas may embrace and strangle the duodenum, or a collection of inflammatory material may seriously compress it. The swelling will, however, be usually less general in pancreatitis than in obstruction, and, even if the bowels will not move, flatus can generally be passed. In case of doubt, exploration may reveal fat necrosis. In perforation of a duodenal or gastric ulcer there will generally have been premonitory symptoms pointing to the disease before the perforation actually occurs, and almost immediately an absence of liver dulness may be found. In acute ptomaine poisoning the history, the more general character of the pain, and the presence of diarrhœa will usually help the diagnosis.

In phlegmonous cholecystitis the symptoms are usually preceded by a swelling and well-marked tenderness beneath the right costal margin, at first distinctly localised and only later extending to the epigastrium and umbilical region, where the tenderness is generally found in acute pancreatitis from the beginning of the illness; moreover, the history of gall-stones will usually be elicited. In

appendicitis the tenderness below, and to the right of, the umbilicus and the swelling in that region usually remove the difficulty created by the pain in both appendicitis and pancreatitis, being frequently felt at first just above the umbilicus. In acute pancreatitis the excruciating pain, at first epigastric but later general, the extremely rapid loss of weight, and the irregular tenderness opposite to, and above, the umbilicus are usually characteristic. Halsted lays stress on two symptoms—the excessive pain and cyanosis of the face and of the abdominal wall. The former symptom is universal, but the latter has not usually been present in the cases we have seen. The urinary test for the "pancreatic crystals" should not be neglected, as a positive reaction has been obtained in all the cases of acute pancreatitis in which we have had the opportunity of employing it. Glycosuria is usually absent, but in two out of forty-one cases of hæmorrhagic and in three out of forty cases of gangrenous pancreatitis Körte found it present.

Treatment.—The pain at the onset is so acute as to necessitate the administration of morphine, and the collapse will probably demand stimulants, which, on account of the associated vomiting, may have to be given by enema. In the early stages the symptoms may be so indefinite that the indications for surgical treatment are often not clear enough to demand immediate operation, but as soon as acute pancreatitis is suspected, as it may be by the combination of symptoms together with the urinary test, the surgeon must not wait until the collapse has passed off, as that may be dependent on septic absorption which can only be relieved by operation. The simulation of intestinal obstruction will probably lead to efforts to secure an evacuation of the bowels and relief to the distension. Just as in perforative or gangrenous appendicitis an early evacuation of the septic matter is necessary to recovery, so, in this equally lethal

affection, an early exploration from the front through the middle line above the umbilicus or from behind through the left costo-vertebral angle is indicated, in order, if possible, to relieve tension, to evacuate septic material, to secure free drainage, and to arrest the hæmorrhage which leads to disintegration and necrosis of the pancreas. The after-treatment will be chiefly directed to combating shock and keeping up the strength until the *materies morbi*, both local and general, can be thrown off. Even if no pus be found no harm should accrue from such an exploration, which can be made in a few minutes through an incision in the middle line above the umbilicus. After establishing the diagnosis by the discovery of a swelling in the region of the pancreas with effusion of blood and associated with fat necrosis, a posterior incision in the left costo-vertebral angle will sometimes enable the diseased organ to be very freely drained for the evacuation of pus and gangrenous material without risk to the general peritoneal cavity and with little danger of retained septic matter, as the drainage will be a dependent one. If, however, the inflammatory collection of the tensely distended and inflamed gland be incised from the front, as is advisable in certain cases, gauze packing and gauze drainage may usually be relied on to prevent general infection of the peritoneum. If there are signs of an obstructed common bile-duct, the gall-bladder should be drained, and if gall-stones be discovered they should be removed, if this can be done without seriously adding to the length of the operation or imperilling life by adding to the shock; otherwise they may be left and removed on a subsequent occasion if free drainage of the bile-passages can be secured. We have had six cases of acute pancreatitis under our care and have operated on four, of which two recovered. Of the two cases where operation was not consented to, and where medical treatment alone was carried out, death

occurred in the first case on the third day and in the second case after a week's illness, attended in both with great pain and incessant vomiting.

In a case of gangrenous pancreatitis in a man, aged fifty-eight, a collection of fluid was opened through the great omentum, above the hepatic flexure of the colon, and a slough of the pancreas was extracted, after which free drainage was established. At the same time the gall-bladder and all the stones within reach were removed, but the common duct was not opened, as the patient was too ill to bear a prolongation of the operation. Fortunately, several small calculi worked back through the tube in the gall-bladder and recovery was not delayed and was ultimately complete. The pancreatic reaction was well marked in this case.

In another case of a young married woman suffering from acute suppurative pancreatitis the viscera were found hopelessly matted together. There was extensive fat necrosis all over the abdomen. A subphrenic abscess containing masses of necrosed fat and dark pus was evacuated. The patient was only temporarily relieved and succumbed on the third day. In this case it would probably have been better to have drained through the costo-spinal angle on the left side as well as from the front, but the patient was so ill that it did not appear to be advisable to do more lest death should occur on the table.

In a case of traumatic hæmorrhagic pancreatitis in a man, aged twenty-eight, drainage through the loin as well as in front was adopted, but did not save life, as at the time of operation peritonitis was already advanced, and involved both the greater and lesser peritoneal sacs.

In another case, of a middle-aged medical man, who was seen with Dr. H. P. Hawkins, the diffuse fat necrosis and adhesions of the viscera and omentum into a dense mass presented a formidable obstacle to complete exploration, but as no evidence of any collection of fluid either in the pancreas or in the lesser peritoneal sac could be obtained, and as no gall-stones could be felt in the gall-bladder or bile-ducts, the peritoneal toilet was performed and the abdomen closed, recovery following and ending in complete restoration to health. It is worthy

of note that in this case the diagnosis was confirmed before operation by the urinary pancreatic reaction.

A case was reported by Dr. Charles D. Muspratt, of a woman, aged forty years, who had been admitted to the Royal Victoria Hospital, Bournemouth, on December 3, 1903, in a state of collapse and suffering from severe abdominal pain with incessant vomiting. The abdomen was opened within twenty-four hours of the onset of acute symptoms and the omentum and intestines in the neighbourhood of the pancreas were found deeply blood-stained with numerous spots of fat necrosis. The pancreas was almost purple and extremely tense. An incision was made into the dark gland and very free bleeding followed which was arrested by ligature. Gauze drainage was employed and complete recovery followed.

This is apparently the first case in which direct incision of the pancreas was adopted, and the operator is to be congratulated not only on having had the strength of his convictions in treating acute hæmorrhagic pancreatitis on the lines of other phlegmonous inflammations, but on the success of such treatment. In a case reported by von Mikulicz in 1903, a patient, under the care of Dr. C. B. Porter, of Boston, was operated on by a deep incision into the inflamed gland, with an excellent result. This is apparently the second case in which the pancreas was deliberately incised during acute inflammation with a successful result. Woolsey gives a summary of three cases of this affection successfully dealt with by laparotomy and drainage. The first two cases were operated on in the early stage—the first on the third day and the second twelve hours after the onset. The first case was a hæmorrhagic one and showed fat necrosis; the second case showed no fat necrosis or bloody fluid, but the latter appeared on the removal of the gauze drain two days after the operation. In the third case there was marked but temporary glycosuria. Dr. C. G. B. Kempe, of Salisbury, on December 11, 1902, excised a portion of the head of

the pancreas affected with acute hæmorrhagic pancreatitis. It was done within two hours of the onset of hæmorrhage. The patient unfortunately died from diarrhœa fifteen days later. The argument that the percentage of mortality will be less if the surgeon waits for the formation of a local abscess is fallacious, as it takes no consideration of the large percentage of those who die before such a favourable result is presented; and, in the second place, many patients never develop a local abscess, the process being diffuse from the onset. The high mortality of early operation in acute cases is due to the fact that in many of these fatal instances intestinal obstruction was suspected and the collapsed patients were subjected to a prolonged search for the seat of the supposed lesion. Of fifty-nine reported cases of operation during the acute stage, twenty-three recovered; these include the cases just described. Although this is a large mortality, it must be borne in mind that the disease is a lethal one and usually ends in death if not treated surgically. The lessons which one may learn from recorded cases are not to wait until the system is over-weighted with absorbed poison before operating and not to spend too long a time over the operation.

SUBACUTE PANCREATITIS

Although no hard-and-fast line can be drawn between acute and subacute pancreatitis, yet the less acute onset, the longer course, the limitation of the suppurative process by lymph barriers, and the much more hopeful outlook as the result of treatment present so many differences that clinical observers will acknowledge that such a division is desirable, from the point of view of both diagnosis and treatment. Acute pancreatitis seems to bear the same relation to subacute pancreatitis that a diffuse mastitis does to a simple abscess of the breast, or a diffuse suppurative parotitis to a simple parotid abscess.

It may have a more or less sudden onset, with acute pain and vomiting, and may be associated with constipation, but collapse is not a marked symptom and is, as a rule, absent. The upper abdominal region does not become so rapidly distended and vomiting is less severe and less prolonged. At other times, and this is generally the case, the onset is more gradual, though the symptoms may be similar. As gall-stones are the usual cause of this form of pancreatitis, a history of intermittent attacks of spasms, at first without and later accompanied by jaundice, will be elicited, and before the onset of pancreatic trouble the symptoms of infective cholangitis, in the shape of rigors with deepening of jaundice and with intermittent fever, will generally be found. Tenderness over the pancreas is well marked, and on account of the tympanites being less than in the acute form, it may be possible to feel the swollen gland, especially under an anæsthetic, and as the case progresses a definite tumour often develops. Constipation gives place to diarrhœa, and pus or blood may be noticed in the stools, which have a very fœtid odour and usually contain fat and undigested muscle fibres. The pulse is not so seriously affected as in the acute form and the temperature is more irregular. The temperature may reach 104° or 105° F. and yet the pulse may only vary between 70 and 110. The morning temperature may be normal and the evening temperature high for several days or even weeks. Rigors or chills usually occur and may be repeated from time to time. The pain occurs in paroxysms, but there is also a constant dull pain at the epigastrium. The patient may lose the more urgent symptoms and appear to be really improving, but the loss of flesh and feebleness continue, and relapses usually occur, leaving the patient each time more and more feeble until death supervenes from asthenia. Albuminuria is pretty constant, but glycosuria is rarely present. The pancreatic reaction in the urine is, as a rule, well

marked. If an abscess develop, the pus may form a tumour projecting in the superior abdominal region and forming a tender swelling behind the stomach, or perhaps coming to the surface above or below that viscus; or it may burrow into either loin, forming a perirenal abscess, or passing under the diaphragm it may form a subphrenic abscess. Occasionally the pus may follow the psoas muscle and form a subperitoneal abscess in the iliac region, or even passing over the brim of the pelvis it may collect in the left broad ligament.

Sometimes the abscess bursts into the stomach and is vomited, or into the bowel and is voided per anum, after

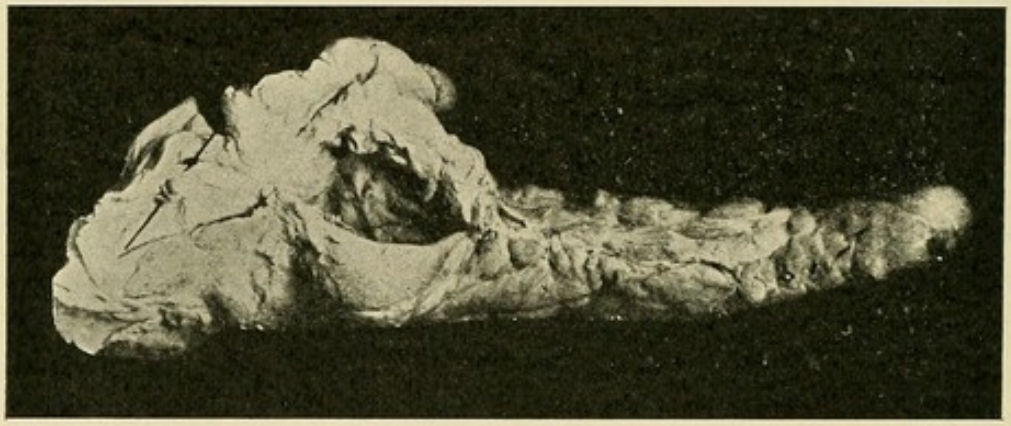

Fig. 130.—Abscess of the pancreas.

which diarrhœa may continue and pus may be seen from time to time as any fresh collection forms and bursts. With the evacuation of the abscess, relief occurs for a time and the temperature improves, but relapses usually take place and a mild form of septicæmia persists with a hectic temperature. Death is the usual termination unless an operation be done, though spontaneous recovery may possibly occur after a tedious and prolonged illness should the abscess burst into the bowel or be otherwise safely evacuated.

For the diagnosis of subacute pancreatitis in its initial

stages little need be added to what has already been said when considering suppurative catarrh and acute phlegmonous pancreatitis. The presence of a tumour or of a diffuse epigastric swelling behind the stomach will be generally found, or if epigastric tenderness prevents palpation, an anæsthetic will enable the swelling to be felt. There is usually fever of a septic type. The presence of leucocytosis and the discovery of the pancreatic reaction in the urine will afford valuable aids to diagnosis. As soon as an abscess forms it may reach the surface above or below the stomach, in either loin, in the left iliac region, under the diaphragm, or even in the pelvis, and will require differential diagnosis from other conditions leading to a collection of pus in those situations, such as chronic perforative gastric or duodenal ulcer, suppurative cholecystitis, splenic abscess, perirenal abscess, spinal abscess, glandular abscess, etc.

Treatment.—The subacute form of pancreatitis is more amenable to treatment, as the indications are so much more definite and there is more time for careful consideration. Though it has usually been attacked only when an abscess has formed and is manifestly making its way to the surface, yet there is no reason why in some cases surgical treatment should not be adopted at an earlier stage. As in the acute condition, morphine may be required to relieve the pain and to lessen the collapse. Distension, if present, demands attention, and may have to be relieved by lavage of the stomach and turpentine enemata or by the administration of calomel by the mouth. Calomel is also of benefit as an intestinal antiseptic, for which purpose it may be given in small repeated doses followed by a saline aperient. As soon as the constipation is relieved, diarrhœa is apt to supervene, when salol and bismuth, with small doses of opium, may be given. If surgical treatment is decided on, a median incision above the umbilicus will enable the operator to palpate

the pancreas and to locate any incipient collection of pus, which, if practicable, should then be evacuated by a posterior incision in the left or right costo-vertebral angle. If the posterior incision be thought impracticable, the collection of pus may be removed by aspiration and the cavity opened and packed with gauze, which may be brought forwards through a large rubber tube, which procedure will, in the course of from twenty-four to forty-eight hours, establish a track isolated from the general peritoneal cavity.

In abscess of the pancreas, which usually assumes the form of subacute pancreatitis, and which we must distinguish from the acute suppurative pancreatitis where the pus is diffused through the gland or where the abscesses are small and multiple, the suppurating process is limited by a pouring out of lymph, so that should the patient survive the initial more acute stage and discovery of the pus-containing cavity be made, the condition is one decidedly amenable to treatment by drainage. The anatomical relation will readily explain the course along which the pus burrows should it burst through its lymph barriers—for instance, in one case an abscess formed and was opened in the right loin of a young man, aged twenty-four years, that had been mistaken for a perirenal abscess, yet the kidney was quite healthy and the grumous pus had come from the pancreas and passed behind the peritoneum covering the second part of the duodenum. The patient recovered completely. In another case an abscess was opened in the left iliac region that had apparently started from the body of the pancreas and which had burrowed in the same way behind the peritoneum. The patient recovered from the operation, but developed trouble in the left side of the thorax and died suddenly several weeks later. In one case the abscess was subphrenic. In another, where the symptoms were rather acute and the patient was ex-

tremely ill, pus was discovered between the liver and the stomach, and although drainage was apparently complete, the patient succumbed in a few days to exhaustion due to the septic process that had been initiated before the abscess was opened. In two other cases, the sequence of suppurative catarrh, abscesses of the pancreas were successfully drained through a tube in the common bile-duct after removing the gall-stones which had obstructed Wirsung's duct. In one of these cases the patient, a woman, aged seventy-two years, remained quite well, but in the other a man, aged forty years, recovered from the operation, but three months afterwards died from exhaustion, and at the necropsy the empty abscess cavity was discovered in the head of the pancreas, the rest of the gland being affected with chronic interstitial inflammation. In one case—a man, aged thirty-five years—a pancreatic abscess burst into the stomach, setting up acute gastritis, the condition having been proved by an exploratory operation. It was treated by gastro-enterostomy to drain away the foul stomach contents. The patient is now quite well, eight years later. In another case, in a young married woman, aged twenty-six years, the abscess apparently burst into the bowel, and, though recovery was tardy, she ultimately got quite well without operation. The diagnosis was made from the symptoms and by an examination of the swollen pancreas under an anæsthetic and subsequently by the presence of a pancreatic reaction in the urine. It is important in these cases to see that the cause is removed, if that be possible—for instance, gall-stones or pancreatic calculi—so that if recovery occurs there may be no fear of relapse.

It will thus be seen that out of eight cases of abscess of the pancreas, one of which was mentioned under acute pancreatitis, six were operated on, with recovery from operation in five, though in one of the cases the relief was only for a few weeks and in another for a few months.

In the eighth case, which was not operated on, the abscess burst into the bowel and was discharged, the diagnosis having been made by an examination of the tumour under an anæsthetic and by the presence of the pancreatic reaction.

When inflammation of the pancreas has ended in abscess, chronic interstitial pancreatitis will also probably be present, as was shown at the necropsy of one case that died some months subsequently. It is possible that in some cases the interstitial change may be local, though in others it will be general and may then lead to atrophy of the gland and to glycosuria.

A search through literature reveals a considerable number of pyæmic abscesses of the pancreas, but those resulting from subacute pancreatitis have been rarely recorded. Besides seven operations for abscess of the pancreas with two deaths above referred to, there have been seven others recorded with three deaths. Thus, of fourteen cases five died, giving a mortality of 35.6 per cent.

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CHAPTER XVI

CHRONIC PANCREATITIS

In a lecture delivered at the London Medical Graduates' College and Polyclinic in July, 1900, attention was drawn by one of us to chronic pancreatitis as a clinical entity. An opinion was then expressed that although it had hitherto been scarcely, if at all, recognised, except as a pathological curiosity, it was not an uncommon disease. Since that statement was made further experience has still more conclusively demonstrated the frequency with which the disease occurs, and how rarely its presence is recognised in clinical practice. Chronic inflammations of the kidneys, liver, and other organs give rise to symptoms which are described in every text-book; but the no less important and characteristic signs of chronic pancreatitis are, even in the most recent medical and surgical works, entirely omitted, or awarded but scanty and inadequate notice. It is true that the relation of the pancreas to diabetes is now generally recognised, but to wait until glycosuria supervenes before making a diagnosis is to throw away the patient's only opportunity of cure—an opportunity which, if taken sufficiently early, will in nearly all cases restore him to perfect health, and save him from a lingering and painful illness.

There appears to be a general belief in the profession that the symptoms of chronic pancreatitis are so overshadowed by those of other morbid states from which it may arise, or with which it may be associated, that it can rarely be recognised during life as a clinical entity, and that even then it is usually only revealed at operation undertaken for the removal of gall-stones or for other

obstructive condition in the bile-passages. Opie, in his work on diseases of the pancreas (p. 163), states that "the lesion is seldom associated with such definite symptoms as to be recognised during life, and that even at autopsy the condition is frequently overlooked." The former part of this statement does not hold good at the present day; for from the information obtained by a careful examination of the patient, a knowledge of the history of the case, and the results of a chemical and microscopical examination of the excreta, a correct opinion may be formed in a large majority of instances. The latter part of Opie's statement, however, is as true today as when it was written. As evidence of the difficulty that even skilled pathologists have experienced in recognising pancreatic disease by naked-eye examination alone, one need only compare the statistics compiled by Hale White from the Guy's Hospital post-mortem records for the fourteen years 1884–1897, and the results of the microscopical examination of the pancreas in a series of consecutive cases by Bosanquet (page 127). From these it is evident that at present it is impossible to rely on post-mortem records, either ancient or even recent, for precise information as to the frequency with which chronic inflammation occurs, and that "unless a microscopical examination of the pancreas is made, it is frequently impossible to say in any case whether it is normal or not, since in many instances the external appearance of the gland may be almost unchanged in the presence of considerable alteration in its anatomy" (Bosanquet).

The surgeon has considerable advantage over the pathologist in this respect, for he has the opportunity of examining and handling the living pancreas, and, after some experience, he can generally tell the difference between the feel of the normal and diseased gland. A chronically inflamed pancreas is generally swollen and harder than usual. A typical case conveys to the examining hand

the impression of a hard waxen cast. This may be recognised as a general swelling of the whole gland, or as a limited swelling involving the head and body of the gland. The swelling and hardness, especially in the early stages of catarrhal inflammation, are, no doubt, due to engorgement with blood and retained secretion; but as in many cases this will largely disappear after death, the difference noticed in biopsies and autopsies is easily explained. The lobules of the gland have the feeling of being mapped out and differentiated in a manner very different from their state in the ordinary healthy organ. The irregularity and change of consistency is occasionally so marked that, to the inexperienced, it may suggest malignant disease. In fact, in some of the earlier cases of chronic pancreatitis that came under our notice this was the idea that suggested itself on examining the pancreas during operation, and it was only the subsequent uneventful recovery of a number of these patients, followed by an immunity from any further symptoms of disease—an immunity which in some instances has now extended to a considerable number of years—that confirmed the suspicion that the condition was purely inflammatory. The first case occurred in 1890, and the patient, a woman æt. forty-four, is now well, seventeen years later. Since the third case, in 1892, which was confirmed by autopsy and by a microscopical examination, the opportunity has been taken of examining the pancreas in a very large number of cases during operations in the upper abdomen, and in many of these there was little doubt that disease of this organ contributed to, or was the cause of, the symptoms complained of. The marked, and in many cases striking, relief that followed appropriate operative interference conclusively demonstrated the importance of the condition; and we can point to a large number of patients, now in perfect health, who before operation were extremely ill, and in many cases supposed to be suffering

from malignant disease of the pancreas, chronic catarrh of the bile-ducts, cirrhosis of the liver, cancer of the common bile-duct or of the papilla, cancer of the liver, common-duct cholelithiasis, malaria, and other diseases.

The number of cases of chronic pancreatitis reported in the journals since attention was called to the subject in 1900 shows that others are now recognising the condition, and that, where suitable treatment has been adopted,

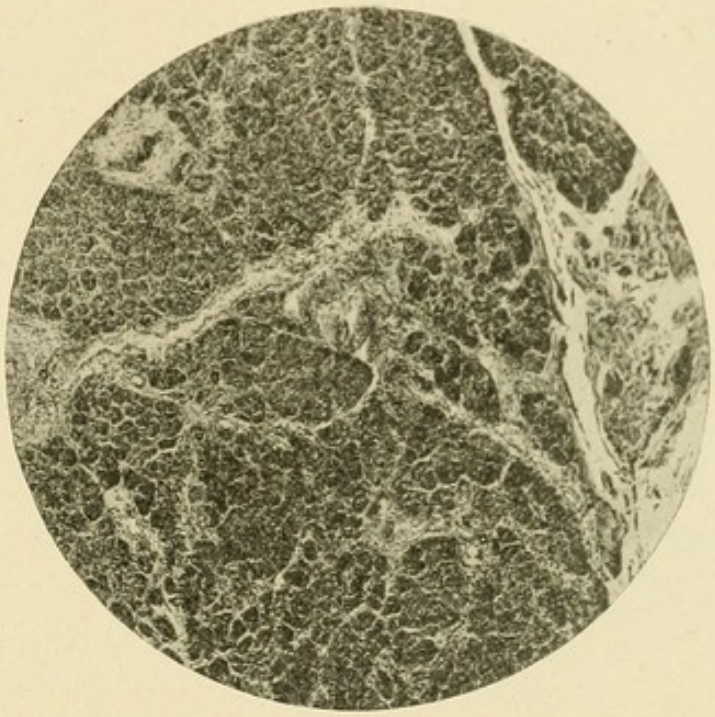


Fig. 131.—Chronic interstitial pancreatitis of the interlobular variety (Santos).

satisfactory results have followed. Chronic pancreatitis has also been reported as occurring spontaneously in the lower animals. Mégnin and Nocard have described the disease in a horse, which, during life, suffered from weakness, loss of appetite, constipation, emaciation, and slight icterus. Post-mortem the pancreas was found to be indurated, the duct was dilated and filled with albuminous material, and the common bile-duct was compressed, there was also catarrh of the salivary duct.

The results of chronic inflammation of the pancreas, as seen on the post-mortem table and following experiments on animals, may be divided histologically into: (1) Chronic interstitial interlobular pancreatitis; (2) chronic interstitial interacinar pancreatitis; (3) cirrhosis of the pancreas.

In the interlobular form of chronic interstitial pancreatitis the normal loose connective tissue between the lobules of the gland is converted into dense sclerotic material, the glandular tissue is compressed, and replaced from the periphery of the lobule, by newly formed connective tissue, the normally obscure lobules becoming distinctly defined.

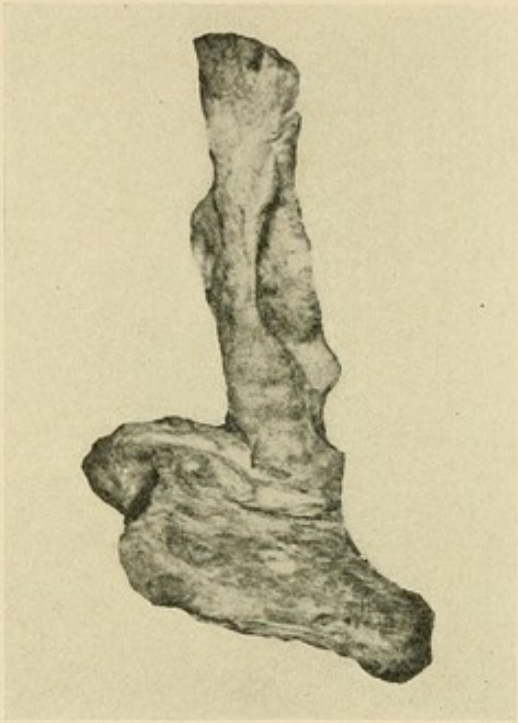


Fig. 132.—Fibrosis of the pancreas (St. Thomas' Hospital Museum, 1413 a).

In the interacinar variety a diffuse network of irregular fibrous tissue is found separating the glandular acini, and in some instances penetrating between the individual cells, while the interlobular tissue is comparatively little affected. The gland is tough rather than hard, and the nodular character seen in the interlobular form is lacking.

Cirrhosis of the pancreas is the final stage of either interlobular or interacinar pancreatitis, but it more commonly occurs as a result of chronic interlobular inflammation, of which glycosuria is a rare sequel, not occurring till the lesion has so far advanced that the glandular acini are

almost completely destroyed, and the vascular supply of the islands of Langerhans is seriously interfered with by the pressure of the newly formed fibrous tissue. In the interacinar form, on the other hand, the cell islands are involved at a very early stage, diabetes quickly supervenes, and it may prove fatal before the cirrhosis has become very marked. A marked new-formation of fibrous tissue in the pancreas appears to be a comparatively late result of chronic inflammation, and unless this fact is borne in mind a very incomplete conception of the condition is liable to be formed.

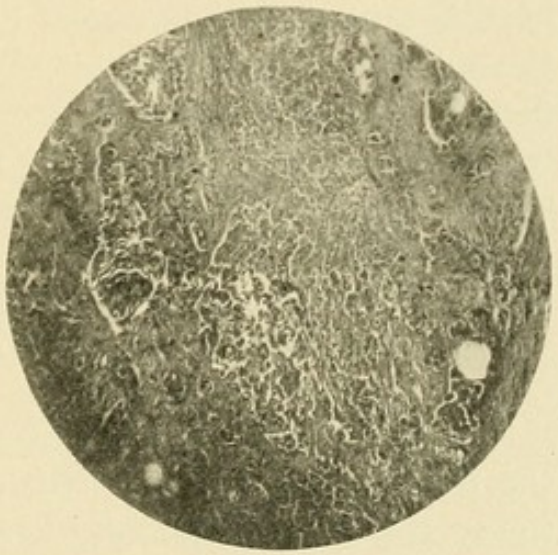


Fig. 133.—Cirrhosis of the pancreas (× ca 40).

Experimental ligature of the ducts in animals has shown that inflammatory atrophy and degeneration of the secreting parenchyma precede and accompany the formation of the new fibrous tissue which takes place, and in chronic pancreatitis due to obstruction of the common duct in man the sequence of events is no doubt the same. In the early stages the organ will be engorged with blood and retained secretion, the parenchyma will show cloudy swelling and other degenerative changes, there will be some leucocyte infiltration, and the ducts will be dilated; but although such an organ may during life be distinctly enlarged and hardened, after death it may appear to be normal or nearly normal to the naked eye, and even microscopically will show no increase of fibrous tissue.

The fact that obstruction of the pancreatic duct with

damming back and infection of the secretion gives rise to chronic pancreatitis has already been mentioned. In practice this is by far the most common cause of the disease, and it is found to be due in most cases to the lodgment of a gall-stone in the lower portion of the common bile-duct. The reason for the association of the two conditions is obvious when the anatomy of the parts is considered.

The common bile-duct, starting by the junction of the cystic duct and hepatic duct, courses along the free border of the lesser omentum associated with the portal vein and hepatic artery; it then passes behind the first portion of the duodenum, and soon comes into relation with the pancreas, which it either grooves deeply, or passes through or behind, before it pierces the wall of the second part of the duodenum, where it empties into the diverticulum of Vater along with the duct of Wirsung. It may be divided into four portions: (*a*) The supraduodenal portion, (*b*) the retroduodenal portion; (*c*) the pancreatic portion; (*d*) the intraparietal portion.

The supraduodenal and the retroduodenal sections of the duct are unimportant for our present purpose, but the relations of the pancreatic and the intraparietal portion of the duct require careful consideration.

The fourth, or intraparietal, segment of the common duct comprises all that portion of the canal contained in the thickness of the wall of the duodenum. It passes obliquely through the muscular coat of the intestine, and then dilates into a little reservoir underneath the mucous membrane into which the main pancreatic duct also opens, known as the ampulla of Vater. The ampulla opens into the duodenum by a little round or elliptical orifice, which is the narrowest part of the bile-channel. The mode of formation of the ampulla of Vater and the termination of the common and pancreatic ducts are liable to at least six variations. These have already been

considered in connection with the anatomy and anatomical abnormalities of the gland, but as they have such an important bearing on the subject of chronic pancreatitis it will not be out of place if they are again summarised here in this connection.

The first type is the classical one, which is described above. In the second type the pancreatic duct joins the common duct some little distance from the duodenum, the ampulla of Vater is absent, and the duct opens into the duodenum by a small, flat, oval orifice. In the third type the two ducts open into a small fossa in the wall of the duodenum, while the caruncle and the ampulla of Vater are absent. In the fourth type the caruncle is well developed, but the ampulla is absent, the two ducts opening side by side at the apex of the caruncle. In the fifth type the common bile-duct opens along with the duct of Santorini, and Wirsung's duct enters the duodenum separately. In the sixth type the pancreas has three separate ducts opening into the duodenum, one only accompanying the common bile-duct.

It will be seen that, while the normal termination and the second variety of termination of the ducts will favour the onset of pancreatitis in case of common-duct cholelithiasis, the variations 3 and 4, in which the two ducts are separate, will possibly save the patient from the serious secondary pancreatic troubles, and in variation 5 and 6 a small portion only of the gland will become infected.

But the pancreatic ducts themselves are also subject to great variations that may influence the course of events. The result of observations by Opie on 100 cadavers (Figs. 30, 61) in which the ducts were injected and photographed was as follows:

In ninety-nine specimens the two ducts were united; in ten, two wholly independent ducts entered the intestine.

1. Of the ducts in anastomosis:
   (1) Duct of Wirsung was the larger in eighty-four.
      (*a*) Duct of Santorini patent in sixty-three.
      (*b*) Duct of Santorini not patent in twenty-one.
   (2) Duct of Santorini larger in six.
      (*a*) Duct of Wirsung patent in six.
      (*b*) Duct of Wirsung not patent in any.
2. Ducts not in anastomosis in ten.
   (*a*) Duct of Wirsung larger in five.
   (*b*) Duct of Santorini larger in five.

In 89 per cent. the duct of Wirsung was larger than the duct of Santorini, while in 21 per cent. the duct of Santorini was apparently obliterated near its termination. In six cases the duct of Santorini was larger than the duct of Wirsung. In all cases where the duct of Santorini was patent it diminished in size towards the duodenum. Thus the duct of Santorini cannot be relied on in many cases to supplement the duct of Wirsung, if it be obstructed; moreover, the duct of Santorini, even if patent and communicating with the duodenum, may itself be compressed by a moderate-sized gall-stone passing down the pancreatic portion of the common duct.

It might be argued that if the two ducts communicate, why should not the duct of Santorini act as a safety-valve to the duct of Wirsung when it is compressed, and thus free the pancreas from the retained secretion, which is in danger of becoming septic? It will be seen that in only half or less than half of all cases will the duct of Santorini act as a safety-valve if the duct of Wirsung is obstructed, for although in 63 per cent. of cases the duct opens at the same time into the main channel and into the intestines, yet in probably less than half of these is the anastomosis efficient as a through channel.

The reasons why gall-stones in the common bile-duct do not always produce pancreatic inflammation are:

(*a*) Some gall-stones are so large that they never

reach the pancreatic portion of the duct, but remain in the supraduodenal portions of the common duct, producing jaundice but no pancreatitis.

(*b*) In some cases the bile-ducts and pancreatic ducts open by separate orifices, and any gall-stone passing down the common duct will not then necessarily compress or occlude the pancreatic duct.

(*c*) In exceptional cases the duct of Santorini is the principal outlet for the pancreatic fluid, it being of such a size as to afford a safe outlet to the secretion even when the duct of Wirsung is obstructed.

The course of the third or pancreatic portion of the common duct is also of great interest, for if it passes through the gland, any congestion or swelling of the head of the pancreas will, by the pressure it exerts on the common duct, tend to induce jaundice and its various sequelæ; whereas if it passes behind, and not through, the head of the gland, it will escape from pressure when the pancreas is inflamed.

The passage of the common duct through the substance of the pancreas in a certain proportion of individuals probably explains many of the cases of so-called catarrhal jaundice, which may come on as an extension from gastro-duodenal catarrh, or in the course of various ailments, and which it is not unlikely are often dependent on catarrhal inflammation and swelling of the pancreas, leading to pressure on the bile-ducts. Such are many of the cases of acute jaundice, especially the form coming on in young subjects, and which usually clear up under medical treatment. They are truly pancreatic and not biliary in origin, and some of these cases pass on from the simple congestive or catarrhal form to true interstitial pancreatitis. The so-called chronic catarrh of the bile-ducts leading to persistent jaundice is nearly always due to chronic pancreatitis, the obstruction to the flow being outside and not inside the common duct.

As the duct is completely embraced by the pancreas in 62 per cent. of all cases, we may conclude that in about that proportion of cases a swelling of the head of the pancreas will produce jaundice, and, as supporting this view, this percentage corresponds with our clinical and pathological investigations of the urine of pancreatic cases, when associated with gall-stones in the common bile-duct.

A gall-stone passing down a duct thus embraced by the pancreas is almost certain to exert pressure on the gland, and the resulting inflammatory changes may in their turn give rise to compression of the duct, which will result in jaundice that may persist long after the gall-stone itself has passed.

Occasionally the ducts are obstructed by other causes than gall-stones. A growth occurring in the ampulla of Vater, or in the papilla, will interfere with the free flow of the pancreatic secretion, and may give rise to catarrh of the ducts and chronic pancreatitis. An impacted pancreatic calculus, or stenosis of the duodenal opening of the duct following ulceration, will also produce a similar result; and recently a case has been reported in which a portion of hydatid membrane was the obstructing agent.

How far the pancreatic lesion in these obstruction cases is to be attributed to the irritating action of the retained secretion, and how far to the associated bacterial infection, is difficult to say, but it is probable that in all cases the latter plays an important part. Even when the blocking of the ducts is complete, and no direct communication between the micro-organisms in the duodenum and the stagnant secretion appears to be possible, the inflamed walls of the duct present a ready path for the passage of infection. This has been proved in the bile-passages by aseptic ligature of the common duct. Absolutely complete blocking of the duct is, however, very uncommon, except in cancer cases, for bile-pigment can

be found chemically in the fæces in nearly all other cases, even when the stools are free from colour to the naked eye.

Chronic pancreatitis may result from a direct extension of a duodenal catarrh to the pancreatic ducts, and this association of chronic pancreatitis with duodenal catarrh is not at all uncommon. It has been shown experimentally that by injecting fæcal material or bacillus coli into the pancreatic ducts, or by providing a channel, such as an absorbent thread, by which organisms may enter from the bowel, pancreatitis is produced; and that after some time the gland, which is constantly being infected by a permanent channel, eventually becomes sclerosed. We have had the opportunity of investigating a considerable number of cases in which pancreatitis has followed chronic gastric or gastro-intestinal catarrh and duodenal ulcer, and in many of them the condition has been relieved by operation.

The pancreatitis which is occasionally met with as a sequel of typhoid fever is probably due to a specific infection occurring in a similar way, though infection by way of the blood and changes due to toxæmia cannot be excluded. In support of this hypothesis is the fact that typhoid bacilli have been recovered from the bile in the common duct and gall-bladder in some cases where operation has been undertaken.

Influenza and some other zymotic diseases are also occasionally followed by inflammation of the pancreas. In these cases infection may take place by way of the duodenum, or possibly through the blood.

The chronic infections, tubercle and syphilis, may also give rise to pancreatitis. In the former chronic inflammatory changes may be found in the absence of definite tuberculous deposits, and the experiments of Carnot with tubercle bacilli and tuberculin in dogs suggest that the changes are due to toxic substances circulating in the blood, rather than to the direct effect of the bacillus in

the gland. It is probable that syphilitic pancreatitis is a similar toxic manifestation.

The influence of alcoholism in the production of cirrhosis of the liver is still a debatable point, and similarly its relation to chronic pancreatitis has not been settled. In some cases a history of alcoholic excess can be obtained, but in many this is not so. It is probable that alcohol is not of itself a direct determining cause, but that indirectly, by the influence it exerts on the circulation and by the production of a catarrh of the duodenum, it may give rise to pancreatitis.

Fig. 134.—Chronic ulcer of the posterior wall of the stomach eroding the pancreas (R. C. S. Museum 2399).

Chronic pancreatitis and cirrhosis of the liver are not infrequently associated. According to the observations of Lefas and Opie, chronic pancreatitis may accompany either atrophic or hypertrophic cirrhosis, but while in the former the gland is enlarged and the newly formed fibrous tissue interacinar in distribution, in the latter no marked increase of size takes place, and it is the interlobular tissue that is increased in amount and density. It is not uncommon to find both diseases present in long-continued obstruction of the common duct by gall-stones.

In that peculiar condition hæmochromatosis, the pancreas is affected, and chronic interacinar pancreatitis folows the deposit of pigment and associated atrophy of the gland cells.

As in the kidney and other organs, an increase of fibrous tissue occurs in the pancreas in general arteriosclerosis

and endarteritis, and it is possible that the moderate increase found microscopically in a certain number (10 per cent. of Bosanquet's cases) of patients over forty years of age may be attributed to this cause, but that it is not a common cause is shown by Opie's investigations.

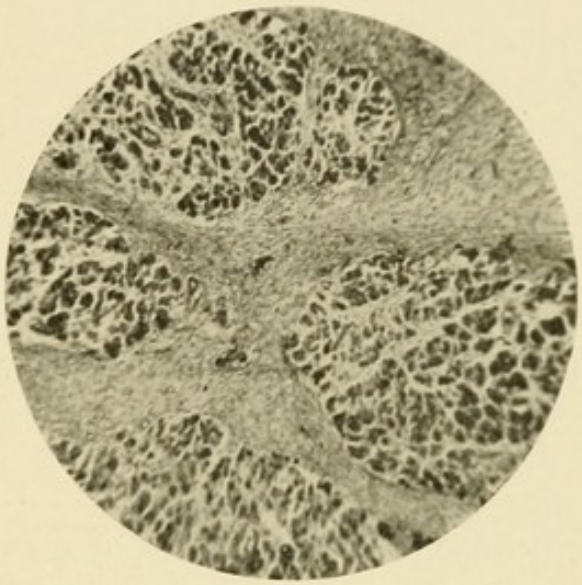


Fig. 135.—Section of the pancreas in the neighbourhood of an adherent gastric ulcer, showing the secondary interstitial pancreatitis (× 40).

Occasionally one meets with chronic pancreatitis due to direct extension of the inflammatory process from a neighbouring organ, such as a chronic gastric ulcer eroding the gland.

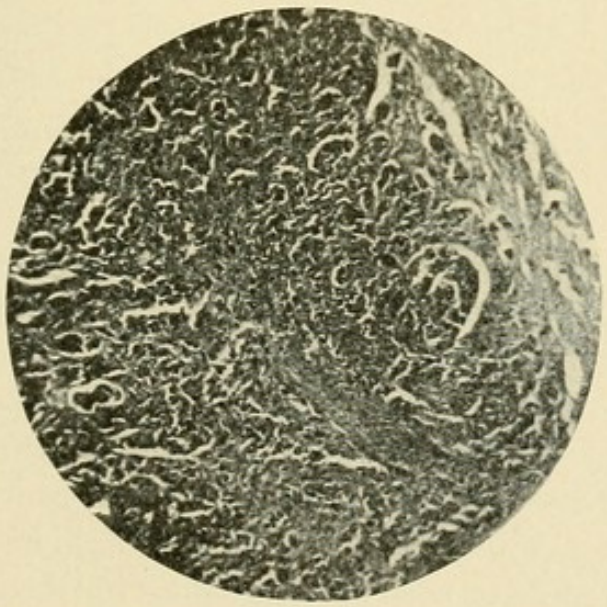


Fig. 136.—Chronic suppurative pancreatitis (× ca 35).

A malignant growth of the pylorus may set up perigastritis and cause the stomach to become adherent to the pancreas, producing well-marked interstitial pancreatitis in the head of the gland, as in a case operated on by one of us recently.

Acute or subacute inflammation of the pancreas, if not ending fatally,

may resolve and be succeeded by chronic inflammatory changes that may ultimately lead to cirrhosis and to a fatal termination at a later date, as was demonstrated in one of our cases of abscess of the pancreas that died three months after operation, in which an opportunity occurred of examining the gland microscopically.

In cystic disease of the pancreas, chronic pancreatitis is nearly always present; in fact, it is probably the compression of the smaller duct by the contracting newly formed fibrous tissue that in many cases gives rise to the cysts.

All the causes of chronic pancreatitis mentioned, except atrophic cirrhosis and hæmochromatosis, are associated with interlobular changes in the fibrous tissue, and from a surgical point of view this is the most important form of chronic inflammation to which the gland is liable, for it is capable of being distinctly benefited by operative interference, if recognized at a sufficiently early stage.

The etiology of the interacinar variety is at present for the most part obscure, although, judging from the early stages at which the islands of Langerhans are affected and the centrifugal character of the new fibrous tissue formation, it is probable that the disease owes its origin to an abnormal state of the blood. It is therefore not likely to prove directly amenable to surgical treatment.

Symptomatology.—The onset of chronic pancreatitis varies with the cause. If it is due to obstruction of the common duct by a gall-stone, there will be a history of painful attacks in the right hypochondrium and in the epigastrium, associated with jaundice and possibly accompanied by fever of an intermittent type. Tenderness at the epigastrium, with some fulness above the umbilicus, will usually be noticed; loss of flesh soon becomes marked, and if the pancreatic symptoms predominate, the pain will pass from the epigastrium round the left side even to the renal and scapular regions.

If, however, the condition arises by direct infection from a duodenal catarrh or from one of the other causes mentioned, and not connected with cholelithiasis, there may be merely an aching in the epigastrium or slight pain not at all pronounced, or the symptoms may come on painlessly, associated with dyspepsia and with slight jaundice, soon becoming more marked; in such cases the gall-bladder may dilate and give rise to a suspicion of cancer of the pancreas which the rapid loss of flesh will tend to confirm. In either case a train of symptoms of a very definite character is set up, and it is difficult to understand how the idea has gained currency that chronic pancreatitis is, as a rule, undiagnosable during life.

Physical examination of the patient will reveal in some few cases a swelling of the pancreas due to tumefaction of the head of the gland; but as the recti are often rigid from the pain and tenderness in the epigastrium, it may be discoverable only when the patient is anæsthetised.

Pain and tenderness, though usually present, may be little marked, but in some cases the pain is paroxysmal and severe, and epigastric tenderness is well pronounced. By distending the stomach with gas, either by means of carbonate of soda and tartaric acid given in separate doses, or by pumping in air through the stomach-tube, the relation of the stomach to the swelling can be readily made out. Resonance on percussion, owing to the position of the stomach, unless the stomach is empty, communicated non-expansile pulsation, and very slight movement on deep inspiration are characteristic.

In the more chronic stages, especially when the disease has reached the cirrhotic stage, if the cause be not gall-stones, a tumour of the gall-bladder is found similar to that met with in cancer of the pancreas. The distension is due to mucus, the bile which first filled it having been absorbed and the backward pressure having prevented

fresh bile from entering the duct. The distension may occur so gradually as to be painless, and the gall-bladder is then free from tenderness, which is less frequently the case in distension due to gall-stones. In jaundice due to a stone in the common duct the gall-bladder is nearly always contracted and not capable of being felt.

Jaundice is not necessarily present at first, although it is usually met with at some stage of the disease, and is often well marked. It may vary from a slight icteric tinge, most marked in the sclerotics, to an intense mahogany hue. In chronic pancreatitis, due to obstruction of the common bile-duct by a gall-stone, the jaundice is frequently very marked, as it is also in those cases where the duct passing through, or grooving, the head of the pancreas is compressed by the swollen gland; when, however, the common bile-duct passes behind the gland, as it does in 38 per cent. of bodies, the patency of the passage may not be seriously interfered with and little or no jaundice be produced. An increase of temperature is, as a rule, associated with acute and subacute pancreatitis, but only rarely in any of the more chronic forms of inflammation, except in those cases where there is associated infective cholangitis, as in obstruction of the common duct by a biliary calculus and infection of the retained secretion, when there may be fever of an intermittent type and ague-like paroxysms.

Dyspeptic disturbances are constantly complained of; they take the form of anorexia with discomfort from flatulency, sometimes offensive eructations, heartburn, nausea, distaste for fats and for meat. Frequent, bulky motions, pale in colour, offensive, and obviously greasy, are usually present in advanced conditions, though in the earlier stages there may be constipation associated with flatulency. Marked and often excessive wasting is often a prominent symptom.

The urine will give a more or less well-marked pan-

creatic reaction according to the extent and intensity of the lesion, and a quantitative chemical analysis of the fæces will show an excess of unabsorbed fat, of which the greater part is unsaponified "neutral fat," particularly if there are advanced interstitial changes in the gland.

Although in any single case we may not have all the symptoms and signs, yet in no case ought we to fail to find evidence of digestive, metabolic, or physical signs if chronic inflammation of the pancreas be present.

No single symptom can alone be relied upon as diagnostic of chronic pancreatitis, but on considering all the available evidence there is not usually much difficulty in forming an opinion. Special stress can be laid upon the progressive wasting, the usual presence of jaundice, the dyspeptic disturbances, the pancreatic reaction in the urine, and the results of the chemical examination of the fæces. Each case, however, has to be considered on its merits, and in making the diagnosis one has to bear in mind the difference in the symptoms produced by the various causes as well as by the variations in the anatomy of the ducts.

In the **differential diagnosis** of chronic pancreatitis the most important conditions to consider are cancer of the head of the pancreas, cancer of the common bile-duct, cancer of the liver, gall-stones in the common duct, and chronic catarrh of the bile-ducts.

In cancer of the head of the pancreas the onset is usually gradual and painless, and the disease usually occurs later in life, generally after forty years of age. It is preceded by general failure of health, and when jaundice supervenes it becomes absolute and unvarying. The gall-bladder is nearly always distended, and may attain a large size. It is not tender on manipulation. The liver enlarges from biliary stasis, but there are no nodules to be felt. In some rare cases a hard nodular tumour may

be felt on the inner side of the distended gall-bladder. The fæces are usually acid in reaction, and contain a large amount of undigested fat, only a comparatively small proportion of which consists of fatty acids. The pancreatic reaction in the urine is negative by the improved method in about 75 per cent. of cases, but in the remaining 25 per cent. a more or less marked reaction, probably due to the associated inflammatory changes, is obtained. Preparations made by the original A-reaction show coarse crystals, soluble in 33 per cent. sulphuric acid in three to five minutes, in many cases, but a typical reaction is not easily obtained and it may be necessary to make several preparations from more than one specimen of urine before they are secured. The extremely rapid loss of weight and strength with increasing anæmia, but without ague-like seizures, is very characteristic, and it is common for there to be an absence of fever, or indeed a subnormal temperature, with a slow feeble pulse, and later ascites with œdema of the lower limbs. The great importance of an accurate diagnosis between cancer of the head of the pancreas and chronic pancreatitis lies in the fact that while the latter is eminently a curable disease when submitted to early operation, the former is not benefited by surgical treatment, which, moreover, is attended by no little danger from various complications.

Cancer of the common duct is rare and is usually associated with gall-stones. If the disease involves the papilla, the symptoms are indistinguishable from those of cancer of the head of the pancreas, except that the urinary pancreatic reaction is more likely to be of the inflammatory type from the associated changes in the gland due to the damming back of its secretion. If the growth is situated above the opening of the pancreatic duct, it will not interfere with the functions of the pancreas; the loss of flesh will not be so rapid, the typical pancreatic reaction in the urine will be absent, and although there may be

an excess of fat in the fæces, this will consist chiefly of combined fatty acids.

Cancer of the liver is distinguished by the irregular enlargement and nodular feel of the organ, the rapid deterioration of health, the less intense jaundice, and the absence of fever and paroxysmal pain. The pancreatic reaction is negative.

A diagnosis of gall-stones may be made by the sequence of a long antecedent history of spasms without jaundice, then a severe attack of pain followed by jaundice, and after a time recurrent pains with increase of icterus associated with ague-like seizures. The absence of tumour is more common in gall-stones than in chronic pancreatitis, though in the latter the gall-bladder may be found contracted at times. The paroxysmal attacks in chronic pancreatitis may be equally as severe as those in gall-stone seizures, but there is usually less pain. The tenderness, however, with gall-stones will be over the gall-bladder, and in pancreatitis at the middle line where the swollen gland can sometimes be felt, especially if the patient is thin or under the influence of an anæsthetic; moreover, the radiating pain in gall-stones is towards the right infra-scapular region, and in pancreatitis towards the left or to the mid-scapular region. When the gall-stones are situated in the first or second part of the common duct, the pancreatic reaction is negative and the fæces alkaline in reaction. The motions, although often containing a considerable excess of fat, do not show the high proportion of neutral fat usually found in pancreatic cases, but are, as a rule, rich in combined fatty acids. When, however, a stone is impacted in the third part of the duct, there is a probability that, in the majority of cases, the pancreas will be inflamed; and when the calculus lies in the fourth part, the pancreas is almost certain to be affected. The diagnosis of chronic pancreatitis from gall-stones is, however, not one of any great practical importance, since the two

conditions are often associated, and the treatment is, at least up to a certain point, the same.

Chronic catarrh of the bile-ducts is characterised by jaundice and loss of flesh, coming on for the most part painlessly, but since it is usually of pancreatic origin, it is not necessary to spend time in discussing it further.

Although the diseases mentioned are the most likely to cause confusion in diagnosis, they are not by any means the only ones for which chronic pancreatitis may be mistaken. More than one patient has been sent to us who, from his colour and recurrent rigors, had been believed to be suffering from ague. The absence of malaria organisms in the blood, the presence of the pancreatic reaction in the urine, a chemical examination of the fæces, and a careful consideration of all the physical signs and symptoms, have quickly revealed the true condition of things, which has been confirmed by operation and the subsequent course of the case.

The blood changes met with in chronic pancreatitis suggesting pernicious anæmia have, in some instances, led to an incorrect view of the case being taken, until the possibility of their being of pancreatic origin was pointed out.

Analysis of the urine and fæces by one of us in several cases diagnosed by various authorities as "hill diarrhœa, psilosis or sprue" has given results that have pointed to the pancreas being involved in the disease, and in one case that was operated on and a cholecystenterostomy performed the condition of the patient was much inproved. The fæces in this case before the operation contained 62 per cent. of total fat, of which 41 per cent. was neutral fat and 21 per cent. combined fatty acid. The urine gave a well-marked and characteristic "pancreatic reaction." After the operation the patient put on flesh, his appetite improved, and at the end of a month the fæces were found to contain 45 per cent. of total fat, 29 per cent. of neutral

fat, and the same amount of combined fatty acid as before, namely, 21 per cent. There was thus not only a diminished amount of fat in the stools, but there was also a much lower percentage of this in an undigested form. His general health had continued good nine months after the operation, and he then stated that, save for an occasional relapse which generally results from some error in diet, he had been free from pain and the fæces had been more nearly normal than for several years previously. A specimen of fæces examined during one of the relapses showed 60 per cent. of fat, of which 42 per cent. was neutral fat and 18 per cent. combined fatty acid. The pancreatic element in at least some cases having the symptoms of sprue has not, we believe, been previously insisted upon, but it is, we think, a point that should be borne in mind in the diagnosis and treatment of the disease.

The **prognosis** of chronic interstitial pancreatitis surgically treated is very favourable, but the longer the disease is left untreated, the more serious the outlook becomes. In some cases it may slowly progress for months or even years, but ultimately the well-marked cases die, either from asthenia or more rarely from hæmorrhage or diabetes. A marked hæmorrhagic tendency usually shows the near approach of a fatal termination, and when diabetes has supervened, the disease is, as a rule, so far advanced that surgical interference is not likely to do more than possibly delay its progress, though a moderate degree of glycosuria need not be a bar to operation, as this may arrest the progress of the disease.

Treatment.—Before considering either the medical or surgical treatment of pancreatitis, the importance of preventive treatment by attention to the causes, some of which, such as gall-stones, are removable by operation in the very early stages with a very small risk, certainly not more than 1 per cent. in skilful hands, must be insisted upon. Duodenal catarrh as a cause of pancreatic

catarrh and of interstitial pancreatitis is remediable by medical treatment; and duodenal ulcer, another cause, if not remedied by careful and thorough general treatment, can be cured by gastro-enterostomy with a very small risk.

If, after a fair trial of general treatment, care in diet, wet packs to the epigastrium, rest, and mild mercurial purges, not too long continued, the symptoms persist, and the signs of failure in pancreatic digestion and metabolism are manifesting themselves, the question of surgical treatment should be seriously considered, especially when the disease is associated with jaundice, for the condition is one that, if not relieved early, will certainly lead to serious degeneration of both the liver and pancreas, and become dangerous to life in several ways.

Rational treatment should aim at the cause, whether that be gall-stones, pancreatic calculi, duodenal catarrh, duodenal or gastric ulcer, alcoholism, or syphilis.

In operating for chronic pancreatitis when medical treatment has failed to relieve, the surgeon must be prepared to do a thorough operation, so as to expose the whole length of the common bile-duct as well as the head of the pancreas. He will then be able to remove the cause should it prove to be a gall-stone, or a pancreatic calculus, or any other removable condition. In the absence of some obvious removable cause, it is advisable to secure efficient drainage of the infected bile-duct and pancreatic duct, either by cholecystotomy or cholecystenterostomy, preferably the latter. Where the pancreatic disease is dependent on duodenal catarrh associated with ulcer of the duodenum, it may be advisable, at the same time that the bile-passages are drained, to perform also a gastro-enterostomy in order to cure the original cause of the disease. Experience has taught that if the cause can be removed at an early stage, an absolute cure is possible; and though complete restoration of the damaged gland

in more advanced cases cannot always be promised, yet an arrest of the morbid process may be looked for, and the remaining portion of the pancreas will be able to carry on the metabolic, and, even if incompletely, the digestive functions of the gland.

Surgical Treatment.—In several of our earlier cases of chronic pancreatitis the abdomen was opened and the biliary ducts and swollen head of the pancreas were exposed and manipulated without finding gall-stones. Whether it was that the manipulation of the parts displaced and pushed on a stone from the common duct into the duodenum, or that the breaking down of adhesions relieved tension, the fact remains that in a number of such cases the patients completely recovered and remained well. This was the course of events in the following case:

The patient, a woman, aged forty-four years, had for some time been suffering from deep jaundice with considerable pain, some irregular fever, digestive disturbance, and emaciation. At the operation on June 22, 1890, after separating a number of adhesions, a tumour of the pancreas embracing the lower end of the common duct was found, which at the time was thought to be malignant. The tumour was freely manipulated in order to ascertain if any gall-stones were present in the common duct, but none could be felt, and as the gall-bladder was contracted and there was some tendency to hæmorrhage from numerous small points, the investigation was not carried further and the abdomen was closed. Whether any concretion was pressed onward into the duodenum it is impossible to say, but the patient made a good recovery from the operation and within a few months she had regained her health. A letter received from her medical man states that she is now, fourteen years afterwards, in very good health.

But in other cases of this kind, although the patients have recovered from operation and apparently become restored to health, an examination of the urine years

later has shewn the presence of the pancreatic reaction, and in some cases there has been glycosuria due to a seriously damaged pancreas. The following is a case in point:

Mr. D——, aged forty-two, had an attack of pain in the right hypochondrium ten years ago, but no jaundice. He had been free from attacks up to six weeks before seeing one of us, when he had a severe attack of pain in the right hypochondrium, radiating to the back and shoulders, accompanied by rigors and vomiting and followed by jaundice. The jaundice had persisted up to the time of his being seen, but then no swelling could be felt. An exploratory operation was performed on October 27, 1898, when a mass, thought to be growth in the head of the pancreas, was discovered. The patient made a good recovery with gradual relief to the jaundice. The enlargement of the head of the pancreas was doubtless chronic pancreatitis, as it was too soft for scirrhus. It was very freely manipulated in order to ascertain if there was a gall-stone in the termination of the common bile-duct, and this may possibly, though if so, unconsciously, have dislodged an obstruction, leading to relief of the jaundice. A specimen of his urine was obtained in 1904, and although he was reported to be quite well, this was found to give crystals by the "A" reaction, which dissolved in 33 per cent. sulphuric acid solution in half a minute, and to contain sugar in fair quantity.

This, along with other cases, shews that it is unwise not to thoroughly drain the bile-ducts in all such doubtful cases, and if cholecystenterostomy is not performed, drainage ought to be continued until the bile becomes free from organisms and its normal route is free from obstruction.

In certain cases, doubtless, recovery occurs without operation, and we have notes of one case where a gentleman of advanced age had deep jaundice associated with glycosuria and with well-marked pancreatic reaction in the urine, pointing to the case being one of pancreatic

diabetes. Under general treatment, combined with massage, he regained his health, and is now said to be quite well. In this case it is quite possible that the massage may have dislodged a concretion which was blocking the common bile-duct and the pancreatic duct, but as no search was made in the fæces, this cannot be proved. As the patient lives abroad, we have not been able to test the urine, which will probably still contain glucose.

This case raises the question whether operations ought to be declined because of the presence of a small amount of sugar in the urine. In future, should the patient's condition be fair, one would feel inclined to recommend operation in order to remove the obstruction, and, by drainage, to arrest the pathological process going on in the pancreas.

It was only after the complete and perfect recovery of a case of interstitial pancreatitis in 1891, after the performance of cholecystotomy by one of us, that the indication for drainage of the bile-passages in inflammatory swelling of the head of the pancreas was made manifest. The following is a report of the case:

The patient, a man, aged fifty, was deeply jaundiced and supposed to be suffering from a gall-stone in the common duct, but on exploration on February 17, 1891, no biliary concretion could be felt, though a swelling of the head of the pancreas was found. The patient recovered after a simple cholecystotomy and regained his health, but we have not been able to trace his subsequent history.

In 1892 came the first opportunity of actually proving the true pathological condition by a microscopic examination of the head of the pancreas. The following is a description of the case:

The patient was a man, aged thirty-two, who was seen in April, 1892. He was extremely ill and emaciated at the time, and suffering from deep jaundice and great prostration with dilatation of the gall-bladder. Operation

was undertaken too late and death resulted from shock and exhaustion on the second day. A necropsy revealed a cirrhotic condition of the head of the pancreas compressing the common bile-duct, there being no evidence of malignant disease (Fig. 137).

Up to this time all the cases were examples of chronic pancreatitis, either independent of cholelithiasis, or in which no gall-stones were present at the time of operation, though one suspected that gall-stones had been the original cause of the trouble in both the first and second cases.

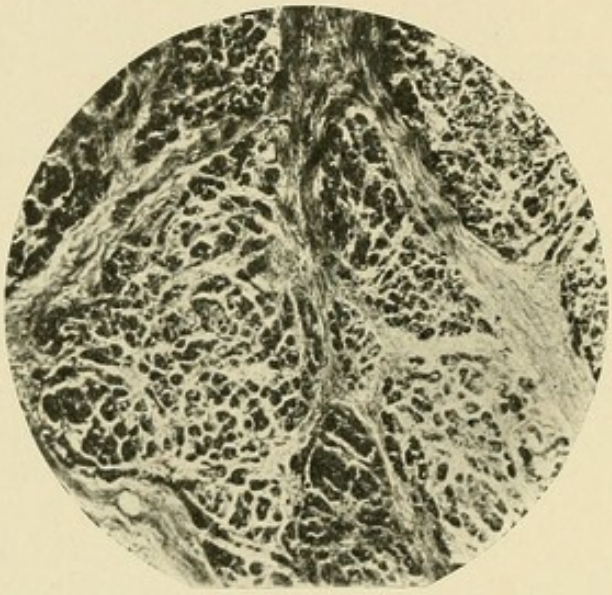


Fig. 137.—Advanced chronic interstitial pancreatitis of the interlobular type (× ca 35).

It was not until 1895 that one of us actually found the associated condition of gall-stones in the common duct with chronic interstitial pancreatitis, and after removing the calculi from the common duct, short-circuited the gall-bladder into the duodenum, by the operation of cholecystenterostomy, after which the patient recovered and was in excellent health three years later. The following is a brief description of the case:

The patient, a woman aged fifty-one, had chronic jaundice and irregular fever, associated with spasmodic pains and great loss of flesh. Operation was performed on July 15, 1895, when gall-stones were removed from the common duct and a hard swelling of the pancreas was felt which was thought to be cancer. The gall-bladder

was connected to the duodenum to establish permanent drainage. The patient recovered and was in excellent health three years later.

This was followed shortly by other cases of interstitial pancreatitis, some associated with gall-stones, while in others there was no evidence of cholelithiasis, but all of which were treated by cholecystenterostomy, which has since been repeated on numerous occasions; at times the short-circuiting operation alone being done, at others the operation being associated with choledochotomy or duodenocholedochotomy.

The following cases will serve as examples:

A man aged thirty-four was seen in 1897. He had had painful attacks resembling cholelithiasis since June of 1896, and deep jaundice since December. The gall-bladder was distended and easily palpated. The patient was extremely ill and emaciated. At the operation on February 25, 1897, the gall-bladder was found to be dilated and surrounded by numerous adhesions, but no gall-stones could be felt. Cholecystenterostomy was performed. The patient made a good recovery and rapidly lost his jaundice. His medical attendant was good enough to write on January 24, 1904, to say that the patient was in good health and had never had a day's illness since his return home, the operation having taken place seven years previously.

A woman was seen who had had gall-stones removed from the gall-bladder three years before, in Canada. She had never been free from jaundice since the operation, and was subject to frequent vomiting. She was much emaciated, the stomach was dilated, and there was marked tenderness over the gall-bladder region. At the operation, on October 18, 1897, very extensive adhesions were found and the pancreas was much enlarged. Cholecystenterostomy was performed, after which she gradually regained her health. Her medical man was kind enough to send word on January 24, 1904, that the operation had been a complete success and that the patient was leading an active life and was well six years after operation.

A female patient was seen on October 20, 1899, who had been suffering for three years from attacks resembling those of gall-stones, each attack being followed by jaundice. During the past fourteen weeks the seizures had been more frequent and severe, and jaundice had never quite cleared away before another attack came on. She had lost flesh and strength considerably and had vomited from time to time between the attacks. Her digestion was much impaired and there was a want of appetite. She had had no rigors and had only slight fever at the time of each seizure. The urine contained abundant lithates and a slight trace of albumin, but no sugar. An examination of the abdomen showed no manifest enlargement of the liver or gall-bladder, but some tenderness over the gall-bladder and at the epigastrium, where there was an indefinite sense of fulness. An operation was performed on the 23d, when, after detaching numerous adhesions, fifteen gall-stones were removed from the cystic and common ducts, but, as a large nodular mass was occupying the head of the pancreas and partly obstructing the common duct, it was deemed advisable to perform cholecystenterostomy so as to make a permanent opening between the fundus of the gall-bladder and the duodenum. The tumour gave the impression that it was malignant. Recovery was, however, uninterrupted, the button was passed on the tenth day, the wound healed by first intention, and the patient immediately began to put on flesh. She returned home within the month and has since been perfectly well in every respect.

A man aged twenty-five was seen on January 11, 1905, on account of deep jaundice with serious deterioration of health, accompanied by loss of weight and strength. He gave a history that he had been out big game shooting in Uganda and had had an attack of fever, from which he had made a good recovery, returning home in September, 1904, in fairly good health. In October he had what he took to be a return of the fever, the attack being ushered in by a rigor, and followed, within a few days, by jaundice, which gradually deepened, but he had absolutely no pain in the abdomen or elsewhere. He lost his appetite forthwith, and speedily began to lose flesh, so that when he was seen his weight was less by a stone than

on his return home. There had been neither sickness nor vomiting since November, and he had had no more rigors. His pulse had been very slow (from 40 to 50) and the temperature subnormal. These symptoms continued up to the time he was seen, when he was found to be suffering from deep, almost black, jaundice, and from anæmia. The liver reached well below the costal margin, almost to the umbilicus, but the spleen could not be felt. A little tenderness was elicited an inch above the umbilicus and half an inch to the right of the middle line, where it was thought a slight fulness could be felt, but this was indefinite. No dilatation of the stomach could be made out, and beyond the jaundice, with the pale motions and dark urine, no other physical signs could be elicited. The motions were bulky, but not frequent, and there was no tendency to diarrhœa. The tongue was somewhat coated. Chronic pancreatitis was suspected and the urine and fæces were examined, the following being the report: Urine—Reaction, acid. Specific gravity, 1.014. Albumin, *nil;* some nucleo-proteid. Dextrose, *nil.* Pentose, *nil.* Maltose, *nil.* Glycuronic acid reaction, negative. Indican, marked reaction. Ferric chloride reaction, negative. Bile-pigment, much. Microscopically, a few bile-stained epithelial cells. "Pancreatic reaction": "A," many fine crystals soluble in 33 per cent. sulphuric acid in one-half to three-quarters of a minute (Fig. 138); "B," some fine crystals soluble in 33 per cent. sulphuric

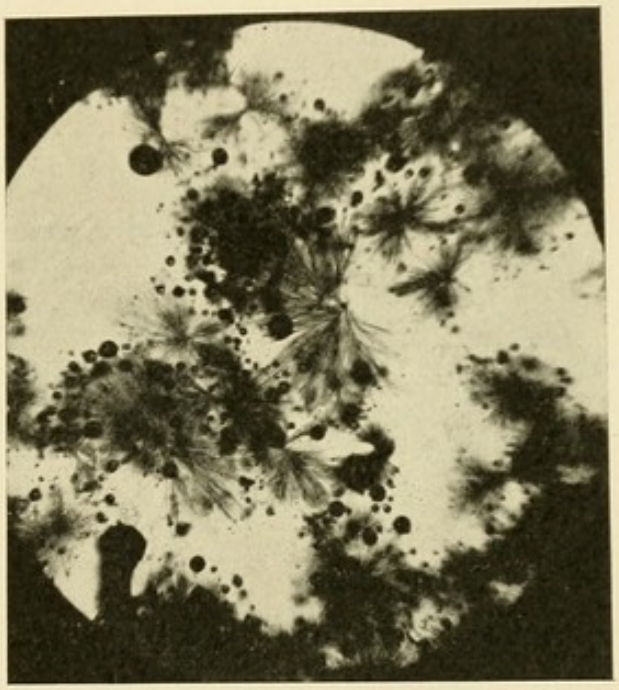


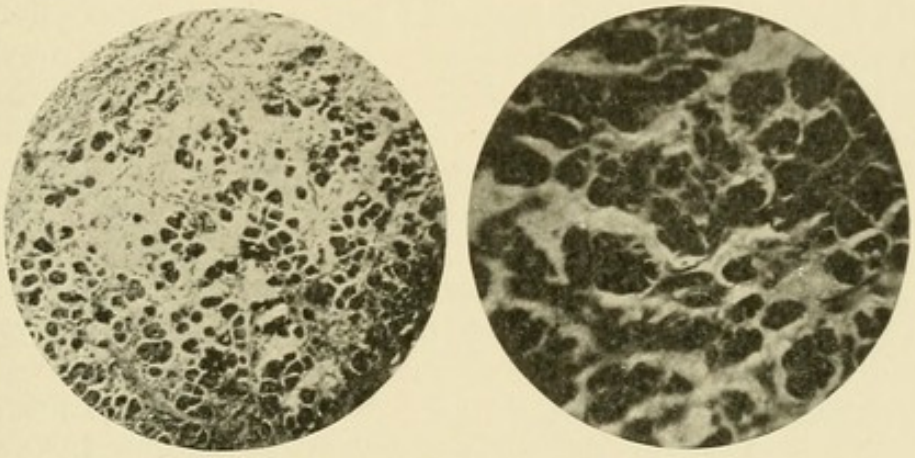
Fig. 138.—Crystals from the urine obtained by the "A-reaction" in a case of chronic pancreatitis (× 190) described in the text.

acid in one minute. Fæces—Reaction, alkaline. Stercobilin, traces. Microscopically, crowds of fat globules, many fatty acid crystals, much vegetable tissue, some partly digested muscle fibre, epithelial cells, and granular débris. Total, fat, 56.8 per cent.; neutral fat, 29.5 per cent.; fatty acids, 27.3 per cent.

These results indicated a pancreatic lesion of an inflammatory nature. The character of the crystals obtained from the urine and the relations of the "A" and "B" reactions suggested that, while the condition was probably of some standing, there was at the time some active inflammation of the gland. The large amount of bile-pigment in the urine, and its almost complete absence from the fæces, together with the high percentage of fat and the presence of muscle fibre in the latter, pointed to an obstruction of the common duct as the probable cause of the condition. The considerable reaction for indican given by the urine suggested that there was some catarrh of the upper part of the intestine.

As medical treatment with rest in bed and care in diet had been thoroughly tried without any benefit, an operation was advised. This was performed at a nursing home on January 16, 1905. On opening the abdomen by a vertical incision through the centre of the right rectus a little ascitic fluid, deeply bile-stained, escaped. The liver was found to be enlarged nearly to the umbilicus. It was dark and mottled, and showed evidences of cirrhosis, apparently due to biliary stagnation. The gall-bladder was thickened, but not greatly distended, though it had evidently been inflamed, as adhesions were found between it and the cystic and common ducts and the neighbouring viscera, stomach, duodenum, and colon. The foramen of Winslow was obliterated by adhesions. The head of the pancreas was much enlarged and widened in area, so that it extended some distance up by the side of the common duct, which it enveloped. A hard nodule could be felt in the head of the pancreas, which hardness could be traced into the wall of the duodenum, and which faded off into the body of the pancreas, the body and tail of the organ being apparently of almost normal consistency. Adjoining the portion of the pancreas, which was stony hard, could be seen a number of lobules of the

pancreas, which were firmer than normal and very definitely outlined, a condition seen in a number of cases of chronic interstitial pancreatitis previously operated on. The localised hardness raised the question as to whether there might be a growth of the papilla extending into the duodenum, or whether there might possibly be a pancreatic calculus impacted in the duct. It was therefore felt desirable to thoroughly explore the pancreas, and to this end the visceral peritoneum was incised over the duodenum and stripped from the pancreas. An incision was made into the indurated area and a portion of the hardened mass was removed. Although very hard, it



a *b*

Fig. 139.—Section of a nodule of pancreatic tissue removed at operation, showing chronic interstitial pancreatitis: *a*, Low power (× ca 37); *b*, high power (× ca 190).

did not cut like cartilage and had not the appearance of a malignant growth. Subsequent microscopical examination showed well-marked interstitial pancreatitis (Fig. 139). No calculus could be found. The incision in the pancreas was then closed by several catgut sutures, and the peritoneum replaced. The duodenum was then opened in the centre of the descending portion, when a hard lobule was felt on the inner side of the papilla, and this proved to be continuous with the stony hard lump in the head of the pancreas. It was suspected that this was an accessory pancreas in the wall of the duodenum. It was not ulcerated, and did not give the impression of being malignant. The common bile-duct was clearly

compressed by the hardened head of the pancreas, and in order to establish drainage of the infected bile the only desirable course seemed to be that of performing a cholecystenterostomy. The opening made for exploration into the duodenum was therefore united to one made in the fundus of the gall-bladder by means of a Murphy button, and the abdomen was closed without drainage. The operation was unaccompanied by hæmorrhage, as chloride of calcium had been given in 20-grain doses thrice daily for three days before operation, and the drug was continued subsequently to operation in 30-grain doses in the nutrient injections for a few days. The after-progress was very satisfactory. The wound healed entirely by first intention, and the jaundice began to diminish visibly within two days of operation. His bowels were moved on the fourth day after a dose of calomel, the motions showing the presence of bile. His appetite rapidly returned, and, after the button had passed on the tenth day, he was allowed to take food freely, his appetite being very keen. At first the motions were bulky, frequent, and offensive, evidently due to the passage of undigested milk. Pankreon tablets were therefore given after each meal, with the result that the food was better digested, and the motions were diminished in number.

An examination of the blood was made on January 26th with the following result: Red corpuscles, 3,472,000 per cubic millimetre. Hæmoglobin, 58 per cent. Hæmoglobin index, 0.58. White corpuscles, 9,965 per cubic millimetre. Proportion of red to white corpuscles, 348 to 1. Differential leucocyte count: Polymorphonuclear white cells, 71 per cent.; small lymphocytes, 22 per cent.; large lymphocytes, 4 per cent.; eosinophile leucocytes, 3 per cent.; mast cells, 1 per cent.

At the end of the third week the patient was able to sit up, and when he was weighed at the month-end he had gained a stone in weight, and expressed himself as feeling well. His blood, urine, and fæces were examined again on February 20th, with the following result:

Blood.—Red corpuscles, 4,634,000 per cubic millimetre. Hæmoglobin, 92 per cent. Hæmoglobin index, 1.0. White corpuscles, 5,855 per cubic millimetre. Proportion of red to white corpuscles, 791 to 1. Differential

leucocyte count: Polymorphonuclear white cells, 70 per cent.; small lymphocytes, 22 per cent.; large lymphocytes, 3 per cent.; eosinophile leucocytes, 4 per cent.; mast cells, 0.5 per cent.

Urine.—Reaction, acid. Specific gravity, 1.022. Albumin, *nil.* Dextrose, *nil.* Pentose, *nil.* Maltose, *nil.* Glycuronic acid reaction, negative. Indican, trace. Ferric chloride reaction, negative. Bile-pigment, faint traces. Microscopically, urates. Pancreatic reaction: "A," a few fine crystals soluble in 33 per cent. sulphuric acid in three-quarters to one minute; "B," a few fine crystals soluble in 33 per cent. sulphuric acid in one minute.

This specimen of urine shows a marked improvement on that examined on January 12th. The pancreatic reaction was only slight, and the amount obtained by the "A" and "B" methods equal, indicating probably the fibrotic changes following the pancreatitis previously found. There was still a faint trace of bile-pigment in the urine, but it was exceedingly slight compared with the large amount present on the last examination. The indican reaction was very much diminished, and was not much more than is at times found in health.

Fæces.—Reaction, alkaline. Stercobilin, a considerable amount. Microscopically, vegetable tissue, granular débris, no fatty globules or fatty acid crystals, no muscle fibre. Total fat, 15 per cent.; fatty acids, 11 per cent.; neutral fat, 4 per cent.

On February 20th, when the patient left the nursing home, his weight had increased to 10 stones 9 pounds, it having been 9 stones on admission. It will be seen that whereas before operation the total fat in the fæces was 56.8 per cent., on February 20th it had diminished to 15 per cent., the fatty acids, which were 27.3 per cent. January 12th, had diminished to 11 per cent. on February 20th; and the neutral fat, which was 29.5 per cent. on January 12th, had diminished to 4 per cent. on February 20th. The blood had also very materially improved, as will be seen on comparing the reports, for as on January 26th the red corpuscles were 3,427,000 per cubic millimetre, on February 20th they were 4,634,000 per cubic millimetre; the hæmoglobin, which on January 26th was 58 per cent., on February 20th was 92 per cent.;

the hæmoglobin index on January 26th was 0.85, on February 20th it was 1.0; the white corpuscles, which on January 26th numbered 9965 per cubic millimetre, on February 26th had diminished to 5855; and the proportion of red to white corpuscles, which on January 26th was as 348 to 1, on February 20th was in the proportion of 791 to 1.

A simple drainage of the gall-bladder by cholecystotomy is frequently unsatisfactory, and cannot be relied on in well-marked cases of obstruction, as the drainage of the bile-passages is not sufficiently long continued. This applies especially to the cases in which the interstitial pancreatitis has persisted for some length of time, in which cases, although a cholecystotomy may lead to a disappearance of the jaundice and the digestive symptoms may be alleviated, the metabolic signs found in the urine many months or even years subsequently show that recovery has only been partial.

The following are examples:

Mr. D——, aged forty-five, had had painful epigastric attacks for twelve months, with vomiting, but no jaundice. There had been deep jaundice since January last, with ague-like attacks, and the patient had lost 2½ stones in weight. Cholecystotomy was performed on March 29, 1898. Thickened duct felt, together with a swelling of the pancreas, thought to be cancer of the head of the pancreas and the common bile-duct. Drainage of the gall-bladder for ten days. The patient made a complete recovery, and in August was apparently quite well, having gained a stone in weight. He was in good health in 1901. Though apparently well in January, 1904, an examination of the urine gave the pancreatic reaction and showed that the original damage to the pancreas had not been completely repaired.

Mrs. D——, aged forty-six, had had spasms for years. Acute seizure in July and three times since. Since July, pain and sickness every two weeks. No tumour felt at any time; jaundiced occasionally after an attack of pain;

lost one stone in weight. She had never vomited blood and never had melæna. There was tenderness over the gall-bladder, but no tumour. Slight enlargement of the head of the pancreas. Cholecystotomy was performed on December 11, 1899. Empyema of the gall-bladder. Many stones removed from the gall-bladder and cystic duct. Adhesions broken down. Nodular condition of the head of the pancreas found. The patient made a good recovery and was well in 1904, though an examination of the urine showed the A and B pancreatic reaction and proved that the metabolic functions of the pancreas were still not normal.

In some cases where operation has been delayed, or drainage of the bile-ducts not performed or not long enough continued, the original interstitial pancreatitis may advance so that the islands of Langerhans become involved, and glycosuria ensues, as in the two following cases:

Mrs. C——, aged fifty-one, who was suffering from persistent jaundice, with periodical pains, and ague-like seizures that had extended over a long period, was operated on in July, 1895, when several gall-stones were removed and others crushed in the common duct. A tumour of the pancreas was felt, which it was thought at the time might be malignant. The gall-bladder was therefore drained into the duodenum by a cholecystenterostomy. The patient completely recovered, and has remained well since the operation, over nine years ago, but an examination of the urine showed there to be an abundance of dextrose, but no acetone or diacetic acid. Pancreatic crystals were obtained by the "A" reaction, which dissolved in three-quarters to one minute, but none could be isolated by the "B" method. This showed that although the patient has been relieved by the operation, and had apparently enjoyed good health, yet that she was living with a damaged pancreas and consequent glycosuria.

A man, aged forty-five, was seen on the 25th of October, 1898. The patient was very deeply jaundiced, and said

that he had lost a stone in weight since the onset of his illness, five weeks before. He gave the history of having had attacks of pain, referred to the region of the gall-bladder, nine years previously, but they were unaccompanied by jaundice and passed off after prolonged treatment. From that time onwards he had been free from attacks of pain up to the onset of the present illness, five weeks before, when he was suddenly seized with severe pain at the pit of the stomach and became jaundiced. The pain had recurred daily and had been so severe as to necessitate his taking morphia. His medical attendant noticed a swelling in the region of the gall-bladder a fortnight after the onset of his illness, and there was all along well-marked tenderness at the epigastrium, with gradually increasing enlargement of the liver. The patient's general health rapidly failed, and the loss of flesh was well marked. When seen he looked pinched and ill, he was very deeply jaundiced, and the urine was loaded with lithates, but contained neither albumin nor sugar. There were well-marked tenderness at the epigastrium and a smooth tumour, which was not very tender, in the gall-bladder region; the liver was enlarged and the edge was smooth and could easily be felt an inch below the costal margin. A diagnosis of gall-stones in the common duct was made and the patient was admitted into hospital. The operation was performed on September 27, 1898. On opening the abdomen numerous adhesions between the gall-bladder and liver, and the pylorus, colon, omentum, and duodenum were found. The gall-bladder was slightly distended, but no gall-stones were felt either in it or in the cystic or common duct. There was, however, a hard nodular swelling of the head of the pancreas, which, at the time, was thought to be malignant. In order to give relief, the adhesions were detached and the gall-bladder was drained by cholecystotomy. On October 28th a letter was sent to his medical man, telling him that we feared the disease of the pancreas might be malignant, but that there was a possibility of its being a chronic pancreatitis. On November 5th another letter was written by one of us, to this effect: "I am pleased to be able to tell you that your patient has improved very much and the jaundice has nearly disappeared. I hope, there-

fore, that the tumour of the head of the pancreas may have been inflammatory, and not malignant. At the time of operation it occurred to me that it was not quite hard enough for a malignant tumour, but under the circumstances I felt it my duty to give you my suspicions." From that time onwards recovery was uninterrupted, and the patient left the hospital with the wound closed, within the month. In December, 1899, the patient called to report himself. He looked perfectly healthy and had gained over a stone in weight since his return home. He had neither pain nor tenderness and he said he felt as well as if he had never ailed anything. The scar was firm, the liver was normal, and there was not the slightest tenderness in the epigastrium or in the gall-bladder region. Five years later the patient was apparently well so far as the local symptoms were concerned, but an examination of the urine showed the presence of glucose and the pancreatic reaction was present, thus pointing to the persistence of chronic interstitial pancreatitis, which had evidently extended and invaded the islands of Langerhans. The urine contained no bile and no albumin, but an abundance of oxalates.

Had the gall-bladder been longer drained in this case or cholecystenterostomy performed, it seems highly probable, arguing from the results of operation in other cases, that the sequelæ above mentioned might have been prevented.

Occasionally, however, the simple operation of cholecystotomy may be sufficient to bring about a cure, as in the following cases:

The patient, a man aged forty-five, was seen on March 19, 1898, the history being that he had been well up to twelve months before, when he began to have painful attacks at the pit of the stomach, ending in vomiting, but not followed by jaundice until an attack on January 1, 1898, since which time he had been deeply and continuously jaundiced. He had also from that time onwards had ague-like attacks, and two days before he was seen he had had within twenty-four hours three of these

seizures, each accompanied by pain. Within a twelve-month he had lost 2 stones 8 pounds in weight. On examining him there was some swelling in the gall-bladder region but no tenderness. The liver was a little enlarged but the margins felt smooth. There was decided tenderness in the middle line just above the umbilicus, and on deep pressure the pain was considerable and an indefinite fulness could be felt. The diagnosis of gall-stones in the common duct was made, and an operation was advised. The patient was operated on on March 30th, when the gall-bladder was found to be slightly distended and surrounded by adhesions to the pylorus, duodenum, colon, and omentum. No gall-stones could be discovered, but there was a well-marked swelling of the head and the first two inches of the pancreas, which, though nodular and irregular, was not very hard. This extended further to the right than normal, so as to cover in the lower end of the common bile-duct. Cholecystotomy was performed. Within twenty-four hours of the operation nearly four pints of very offensive bile were discharged through the tube. A specimen was examined by the Clinical Research Association and their report was as follows: "The bile contains both staphylococci and streptococci, but no bacillus coli communis could be found either under the microscope or in the culture." Fearing that the disease might be malignant, and the patient being so extremely weak and ill, a poor prognosis was given, but in a few days the following report was given: "The patient is progressing satisfactorily, though he is still profoundly weak. Bile has appeared in the motions so that the obstruction is evidently overcome. The bowels have been moved naturally and the patient is less deeply jaundiced and looking better generally." On April 5th he was taking his food well and bile was passing freely in the motions. He had had no recurrence of the shivering attacks. Drainage was continued for fourteen days and the patient returned home on the 20th. The urine was then free from bile and the motions were assuming a natural colour; he was taking food well, gaining flesh, and looking better generally. A guarded prognosis was still given, however, as it was thought that the tumour would prove to be inflammatory and not malignant.

From that time onwards his progress to recovery was extremely rapid, and he was said to be perfectly well in every respect a few months later, and had fully regained his lost weight. Two years later he was still in perfectly good health.

A woman, aged thirty-five, was seen on September 11, 1899, with the history of having been subject to attacks of spasms in the upper abdominal region for twelve years, the intervals between the seizures having varied from a few days to several months, but of late they had become much more frequent, and during the week before she was seen she had had four attacks, all severe ones. The seizures began with pain in the epigastrium accompanied by cold sweats and faintness; the pain passed through the midscapular and to the right subscapular region, and lasted from two to six hours, having to be relieved at times by morphia. Jaundice followed the seizures, and if the attacks recurred frequently it was intensified with each, but if there was a long interval only an icteric tinge remained. Palpation revealed a point of tenderness in the mid-line, one-and-a-half inches above the umbilicus, where there was a sense of resistance with an abnormal fulness, but there was no tenderness over the gall-bladder, nor could any swelling of the gall-bladder or liver be discovered. On September 21st a vertical incision through the right rectus exposed adherent viscera, and, on the separation of the adhesions, a thickened gall-bladder was exposed, but there were no gall-stones in it or in the ducts. The lower part of the common duct was surrounded and overlaid by a well-marked swelling of the pancreas, which was harder than usual, but not sufficiently hard to be mistaken for cancer, though it was somewhat nodular. Cholecystotomy was performed and drainage was carried out for a fortnight. Recovery was uninterrupted and the patient returned home within the month, and she has remained well since.

If the gall-stone causing obstruction be removed by operation from the common duct, and drainage of the infected bile-ducts be effected before the catarrhal has passed into the interstitial form of pancreatitis, a com-

plete cure may be expected even after simple drainage of the bile-ducts, as in the following cases:

A lady, aged thirty-four, had had symptoms of gall-stones for four years, and had been under treatment for ulcer of the stomach, but there had been no hæmatemesis. Four months previously jaundice had come on after an attack of pain, since which time the attacks had been frequent and were always followed by an increase of the jaundice, and by rigors and fever. On one occasion the gall-bladder was distended; when seen there was a slight tinge of jaundice. She had lost 3 stones in weight. There was an absence of enlargement of the liver or gall-bladder, but marked tenderness over the gall-bladder was elicited. Pancreatic crystals were found in the urine and digestive symptoms were present. At the operation, on April 23, 1903, one large calculus was removed from the cystic duct, and some smaller ones from the common duct, by separate incisions in the two ducts. The common duct was sutured and the cystic duct drained. The pancreas was slightly swollen. The patient made a good recovery and remains well.

The explanation of the pancreatitis in these two cases was manifestly the obstruction of the pancreatic duct and infection of the secretion; but the complete recovery after operation showed that the inflammation was probably only catarrhal and not advanced interstitial trouble.

If the gall-stone obstructs the common duct for long, what was at first a simple catarrhal pancreatitis may assume a truly interstitial form, and unless drainage of the bile-ducts is continued for some time or permanent drainage in the shape of cholecystenterostomy is established, relapse will speedily occur. The following case is an example:

Mrs. W——, aged fifty-seven, had had two operations previously in Scotland. On the occasion of the first operation, in September, 1902, a number of gall-stones were removed from the gall-bladder, which was drained

for a few days, but after the wound had healed the attacks had been repeated as before. A second operation was undertaken by the same surgeon without finding anything definite. After the wound had healed, and the temporary drainage had ceased, the attacks again returned, and the subsequent history up to the time of our seeing her was that she had almost daily attacks of pain, followed by slight jaundice, and on five or six occasions, usually at intervals of a month, she had had violent seizures necessitating the use of morphia. About five weeks before being seen by us the pain was so violent as to cause her to faint, and just before coming to London another violent seizure, accompanied by collapse, occurred. A rigor with high temperature, 104° or 105°, had followed each attack, the temperature between the seizures rising nightly to 101° or 102° F. She was rapidly losing flesh and strength. An examination of the urine showed no albumin or sugar, but well-marked pancreatic crystals by the A reaction, which dissolved in from one to one-and-a-half minutes, and a smaller number of similar crystals by the B method, rendering, along with other signs, the diagnosis of chronic pancreatitis certain. At the operation on November 20, 1903, the adhesions were found to be most extensive. There was well-marked enlargement and hardness of the pancreas along its whole length, but it was not nodular. The common duct was carefully examined, but found to be free from concretions, and on opening the gall-bladder a probe was passed through it and the cystic and common ducts into the duodenum. While the probe was in position, the pancreas was manipulated and found to compress the duct, thus accounting for the obstruction. Cholecystenterostomy was therefore performed, the union being effected by means of a decalcified bone bobbin. At the time of operation the gall-bladder was separated from its fissure in the liver in order to make it reach the bowel without tension. For a few days after operation bile was discharged from the torn liver surface in free quantities, but there was no leakage from the newly joined viscera. As the bile obtained a free passage into the bowel, it gradually ceased being discharged from the liver, and the tube was able to be left out at the end of ten days. The wound healed

by first intention and the patient was up at the end of three weeks. She was then able to take and digest her food, and has since been quite free from her old attacks.

After cholecystotomy, the patient may become impatient of the continued drainage and demand too speedy relief. This was well shown in the following case:

A military officer, aged sixty, was seen on the 8th of July, 1904. He was in good health up to May 2d of that year, when painless jaundice developed. He had a feeling of discomfort after food, the jaundice deepened, and he rapidly lost flesh. When seen he was deeply jaundiced, the liver was enlarged, nearly to the umbilicus, and the gall-bladder was distended. He said he had no pain and there was no evidence of ascites or œdema of the legs. As he did not improve at all under general treatment, and an examination of the urine showed many oxalate crystals, and a well-marked pancreatic reaction, and the fæces were acid in reaction, and contained 58.7 per cent. of the dry weight as fat, of which 31.4 per cent. was neutral fat, and 27 per cent. fatty acid, a diagnosis of interstitial pancreatitis was made, and operation was performed on July 20, 1904, when the pancreas was found to be much enlarged and compressing the common bile-duct. There was no positive evidence of malignant disease, as although the glands were enlarged, they were discrete and not nodular. As there was a decided hæmorrhagic tendency, and the patient was too ill to bear a prolonged operation, the enlarged gall-bladder was simply drained by cholecystotomy. The patient made a good recovery and improved considerably in his general health, and the jaundice entirely disappeared. In consequence of our temporary absence on a holiday the patient got uneasy about the persistent discharge of bile and was advised to consult another surgeon, although he had been counselled to bear with the cholecystotomy for at least two months before having anything further done. Despite this advice, and without our knowledge, the gall-bladder was short-circuited into the colon. After the operation he was very much distressed by diarrhœa, and after a time he began to suffer from symptoms of septicæmia with rigors, which

ended in death from pyæmia. At the autopsy the infection of the bile-passages was found to have occurred through the communication with the colon, and the liver was riddled with abscesses. An examination of the pancreas showed a simple interstitial pancreatitis.

Drainage of the common or hepatic duct may have to be performed for jaundice due to interstitial pancreatitis where there is absence or contraction of the gall-bladder, either owing to the gall-bladder having been removed at a previous operation or to its having contracted as the result of gall-stone irritation. This is a much less satisfactory operation than cholecystenterostomy, as drainage of the common duct has to be continued for some length of time and the biliary fistula is a source of great distress to the patient. We have had to drain the common duct in several such cases where it was impossible to relieve the patient in any other way; and in one case it necessitated the biliary fistula being continued for a considerable time.

This brings into prominence the undesirability of removing the gall-bladder as a routine practice in operating for gall-stones, for unless it is seriously damaged or ulcerated, or is the seat of malignant disease, or unless there is ulceration or stricture of the cystic duct, removal is quite unnecessary, and we think it better practice to drain it simply and not to perform cholecystectomy, since on some future occasion, should trouble develop in the deeper ducts or in the pancreas and the gall-bladder be absent, it will be impossible, with few exceptions, to short-circuit the obstruction. Moreover, after cholecystotomy gall-stones have no greater tendency to re-form than they have after cholecystectomy, and should cholelithiasis again develop, it will be in the common duct, a much more serious position than if in the gall-bladder.

The following case affords a good example of the advantage of sparing the gall-bladder in operating for gall-stones:

Mr. T——, aged forty-five, was seen by one of us on July 27, 1905, suffering from jaundice and a biliary fistula. He gave the history that he had been operated on in October, 1904, by a hospital surgeon for suppurating gall-bladder, but that the wound had never healed and a biliary sinus had persisted. He consulted a well-known Continental surgeon, who advised operation. When seen by us he had a temperature of 100° F., and looked ill. He said that he was subject to shivering attacks. His tongue was coated and there was slight jaundice. A biliary fistula was present, which was discharging a small quantity of bile and pus. He had lost weight considerably. The urine showed a well-marked pancreatic reaction and the fæces contained a quantity of fat and muscle fibre.

On July 28, 1905, the abdomen was opened and the gall-bladder was separated from the fistula, which was excised. The head of the pancreas was hard, and evidently the seat of interstitial pancreatitis, which compressed the common bile-duct. No gall-stone could be felt in the common or hepatic ducts. The gall-bladder was therefore connected to the duodenum so as to short-circuit the obstruction. The patient made a good recovery and forthwith began to regain his lost flesh, the jaundice disappeared, and his skin soon assumed a healthy colour.

He called to report himself in January, 1907, and said that he was in perfect health. An opportunity was taken of examining his urine some time after the operation, when it was found to be normal and to show no traces of the pancreatic reaction.

If the common duct is greatly dilated it may be possible to make an anastomosis between it and the duodenum so as to short-circuit the obstruction in the head of the pancreas.

The following case affords an example of choledoch-enterostomy in such a condition:

Miss F——, aged twenty-eight, seen with Dr. G—— in June, 1903. She gave the history that four years previously she had had typhoid fever, since which time she had never been well. A year previously she had an

attack of pain followed by jaundice with some enlargement of the gall-bladder. In January, 1902, she was operated on by Dr. G——. No gall-stones were found, but the head of the pancreas was much enlarged. Cholecystotomy was done and the wound healed within the month. She made a good recovery from the operation, and was apparently well until March, 1903, when she had a recurrence of the jaundice with sickness and pain. She became very ill and rapidly lost flesh. When we saw her together there was some enlargement of the gall-bladder and a distinct cystic swelling over the pancreas, and the urine gave the characteristic pancreatic reaction. On June 4, 1903, an operation was performed by one of us, when a large cyst was found on the inner side of the gall-bladder, containing bile and pus, which was evidently a dilated common bile-duct. No gall-stones were found, but there was some swelling of the head of the pancreas. The gall-bladder was also distended and inflamed, and it was drained by a separate tube. The patient made a good recovery from the operation, and returned home wearing both tubes. She was seen again in October, 1903. Since the former operation there had continued to drain away through the tube in the dilated common duct from 20 to 30 ounces of bile, and from the tube leading into the gall-bladder from 4 to 6 ounces of clear mucus. The patient was thin and feeble, had no appetite for food, and was unable to digest anything beyond a little milk. An examination of the urine revealed the characteristic pancreatic reaction, and the fæces contained muscle fibre and much fat. On the 8th of October a further operation was undertaken, when the head of the pancreas was again found to be much enlarged, but no concretions could be felt in it or in the common bile-duct. The gall-bladder was completely excised and the cystic duct ligatured. The dilated common bile-duct was then connected to the duodenum by means of a decalcified bone bobbin and the wound was closed. The same evening the patient expressed herself as feeling hungry for the first time since her illness began. She straightway began to absorb whatever nourishment was taken, had her bowels moved on the second day, gained strength, resumed her natural colour, and made such a rapid convalescence that she

returned home within the month, having gained 7 pounds in weight. In 1906 a report was received to say that the patient was in perfect health.

Details of the Operation for Exploring the Head of the Pancreas and the Common Bile-duct.—Certain modifications of the operation for exploring the head of the pancreas and the common bile-duct have converted what was formerly a most difficult procedure, involving prolonged manipulation, special appliances, and at least two assistants, into a comparatively simple operation, in the greater number of cases, requiring the help of only one assistant and not calling for the use of any special apparatus. By this method, suggested and put in practice by one of us, the time involved in the operation is reduced considerably, and where adhesions do not give unusual trouble, it is easy to complete the work in from thirty to forty minutes, which not only means a saving of time and fatigue to the operator, but a considerable saving of shock to the patient.

A firm sand-bag should be placed under the back opposite to the liver, which not only pushes the spine, and with it the pancreas and common duct, forwards, but acts like the Trendelenburg position in pelvic surgery by letting the viscera fall away from the field of operation, or the same advantage may be obtained more readily and conveniently by employing an operating table specially designed so as to be able to effect the projection of the liver region forwards. The one we regularly employ is the Guyose-Greville table. A vertical incision is then made over the middle of the right rectus, the fibres of which are separated by the finger, which is the most expeditious and the most effective method of exposing the gall-bladder and bile-ducts; but when it is necessary to open either the common duct or the deeper part of the cystic duct, instead of prolonging the incision downwards,

as was formerly done, it is better to carry it upwards in the interval between the ensiform cartilage and the right costal margin as high as possible, thus exposing the upper portion of the liver very freely. It will now be found that by lifting the lower border of the liver in bulk, so as to rotate it if needful, first drawing the organ downwards from under cover of the ribs, the whole of the gall-bladder and the cystic and common ducts are brought close to the surface, and, as the gall-bladder is usually strong enough to bear traction, the assistant can take hold of it by fingers or forceps, and by gentle traction can keep the parts well exposed, at the same time that, by means of his left hand with a flat gauze sponge under it, he retracts the left side of the wound and the viscera, which would otherwise fall over the common duct and impede the view.

It will now be observed that, instead of the gall-bladder and cystic duct making a considerable angle with the common duct, an almost straight passage is found from the opening in the gall-bladder to the entrance of the bile-duct into the duodenum, and if adhesions have been thoroughly separated, as they should always be, the surgeon has immediately under his eye the whole length of the ducts with the head of the pancreas and the duodenum. So complete is the exposure that, if needful, the peritoneum can be incised, and the common duct can be separated from the structures in the free border of the lesser omentum, but this is not necessary except where a growth has to be excised. By incising the peritoneum passing from the duodenum to the pancreas, the duodenum can be lifted up and the posterior surface of the pancreas and the common bile-duct can be fully exposed. The surgeon, whose hands are both free, can with his left finger and thumb so manipulate the common duct as to render prominent any concrétions, which can be cut down on directly, the edges of the opening in the duct being caught by pressure forceps. The assistant can now take hold

of the forceps with his left hand, as that instrument with the sponge will form a sufficient retractor, since the duct is so near the surface. When the duct is incised there is usually a free flow of bile, which, it must be remembered, is infected, but a gauze swab in the kidney pouch and the rapid mopping up of bile as it flows, by means of sterilized gauze pads, avoid any soiling of the surrounding parts, and, if thought necessary, the bulk of the infected bile can be drawn off by the aspirator, either from the gall-bladder or from the common duct above the obstruction, before the incision into the duct is made. After removing all obvious concretions the fingers are passed behind the duodenum and along the course of the hepatic ducts to feel if other gall-stones are hidden there, and a gall-stone scoop, the only special instrument necessary, is passed up into the primary division of the hepatic duct in the liver and quite down to the duodenal orifice of the common bile-duct, and to ensure the opening into the duodenum being patent, a long probe is passed into the bowel. The incision into the bile-duct is now closed by an ordinary curved round needle held in the fingers without any needle-holder, a continuous catgut suture being used for the margins of the duct proper, and a continuous fine green catgut, or spun celluloid, thread being employed to close the peritoneal edges of the gut. In such cases, where the pancreas is indurated and swollen from chronic pancreatitis, and is likely to exert pressure on the common duct for a time, a drainage-tube is inserted directly into the duct, and the opening closed around it by a purse-string suture, the tube being fixed into the opening by a catgut stitch, which will hold for about a week; but where this is not done, a drainage-tube may be fixed into the fundus of the gall-bladder in the same way, as this drains away all infected bile and avoids pressure on the newly sutured opening in the duct; or, better still, the gall-

bladder may be short-circuited into the duodenum by the operation known as cholecystenterostomy.

So easy is it to remove impacted stones after this method of exposure that a long time need not be spent in manipulating stones impacted either in the cystic or common duct, but the duct can be incised at once, the concretions removed, and the opening closed without damaging the duct by prolonged manipulation. Although there is seldom any fear of leakage or of infection, yet owing to the separation of extensive adhesions, there is usually some tendency to pouring out of fluid in the first twenty-four hours. It is therefore generally advisable to insert a gauze drain through a split drainage-tube, bringing it out by the side of the gall-bladder drain, or, better still, both tubes may be brought out of a separate opening external and posterior to the operation wound, which can then be permanently closed. The wound is closed in the usual way by continuous catgut sutures, first to the peritoneum and deep rectus, next to the anterior rectus sheath, and lastly to the skin. Even in acute or subacute, as well as in chronic pancreatitis, this method is advantageous, as, at the same time that the pancreas is exposed, the bile-ducts can be explored, and if the cause be gall-stones, they can be removed. Should it be necessary to expose the under surface of the pancreas, an extension of the incision downwards gives enough room to raise the transverse colon and to get directly at the body of the pancreas through the transverse mesocolon.

To those having little experience in this operation the modifications described may seem trivial, but to those who have experienced the difficulties of the ordinary operation, a method which enables the pancreas and the whole of the bile-passages to be dealt with close to the surface will be sufficiently appreciated. But the technique of the operation is not the only important part of the

treatment of these serious cases, which require care and thought, not only before and at the time of, but subsequently to operation.

A careful study of the causes of mortality in operations on the common duct, associated with jaundice and pancreatitis, shows that hæmorrhage, either immediate, consecutive, or secondary, cannot be ignored as a danger, and that shock, apart from hæmorrhage, has next to claim our attention. Sepsis is no longer the bugbear that it used to be, thanks to a rigid all-round asepsis, the employment of gauze drainage, and the careful avoidance of soiling the wound by infected bile.

Although there is a greater tendency to bleeding in chronic jaundice from pancreatic disease than when jaundice is due to gall-stone obstruction, there can be no doubt that in all cholæmic conditions the blood becomes so altered that the coagulability is seriously diminished, and that these features demand serious attention before any operation is undertaken in cases of common-duct cholelithiasis. By administering chloride of calcium in the case of jaundiced patients, both before operation, in 30-grain doses by the mouth, and afterwards in 60-grain doses by the rectum daily for several days, the hæmorrhagic tendency can be successfully combated.

It is important to ligature all bleeding points and not to trust simply to forcipressure; and, while in non-jaundiced patients adhesions may be simply separated, in these cases it is preferable to divide adhesions between ligatures where practicable. Where there is persistent oozing of blood from innumerable points, a tampon of sterilized gauze forms a useful means of hæmostasis, and this may be made more efficient by employing at the same time a solution of suprarenal extract to the bleeding surface.

The best treatment of shock is preventive, and to that end it is desirable to lose as little blood as possible, though

shock in operation is not always dependent on loss of blood. The patient is enveloped in a roughly made suit of gamgee tissue, and where he is very feeble, or the operation is likely to be prolonged, it is performed on a heated table. A large enema of normal saline solution with or without stimulant, given from fifteen to twenty minutes before, and the administration of five minims of solution of strychnia, subcutaneously just after the operation, are useful. Expedition in operating is an important factor in lessening shock, especially in abdominal surgery, for it stands to reason that prolonged manipulation and exposure of the viscera in patients so ill as those composing the class of cases which we are now considering must generally be, will be badly borne, for it is not only the work of the surgeon but the deep anæsthesia that adds to the shock, since for the operation to be well and expeditiously performed the muscles must be thoroughly relaxed.

After the operation a pint of saline fluid, with one ounce of brandy, is given by enema, and five minims of strychnia are given subcutaneously in two hours and repeated if desirable. The rectal injection is repeated in two hours, and afterwards every four hours with an ounce of liquid peptonoids added. Subcutaneous injections of saline fluid or intravenous infusion are only rarely required.

Cholecystenterostomy.—The operation of cholecystenterostomy consists in establishing an artificial opening between the gall-bladder and duodenum, jejunum, or colon, preferably the duodenum, at the part lying normally close to the gall-bladder.

Although the conception of the operation occurred independently to Harley, Gaston, and Nussbaum, the first operation was actually performed by Winniwarter, of Liege, in 1880, and a case operated by one of us in

1889 was the first cholecystenterostomy performed in Great Britain.

Since 1889 we have performed the operation forty-eight times, and for the following conditions:

1. Interstitial pancreatitis compressing the common bile-duct.

2. Biliary fistula, due to stricture of the common bile-duct, or to compression of it by a swollen and inflamed pancreas.

3. Cancer of the head of the pancreas, where relief of the urgent symptoms appeared to be desirable.

A recent statement, to the effect that cholecystenterostomy is a very serious operation with a heavy mortality, is clearly incorrect when performed for non-malignant conditions, if the operation is properly carried out and with all necessary precautions.

The following statistics shew the results in our practice:

The operation has been performed in thirty-nine cases for chronic interstitial pancreatitis, with two deaths, and in ten for cancer of the pancreas, with seven deaths. The cause of death in the two fatal cases of chronic pancreatitis was in no way connected with the operation, for in one death occurred from acute nephritis, with suppression of urine and uræmic convulsions, without apparent cause, after the patient was apparently well and the wound had been soundly healed for a week, and in the other there was, in addition to the pancreatitis, suppurative cholangitis and abscess of the liver. The very high mortality in the cancer cases clearly proves that operative interference is highly undesirable and that every means should be taken to diagnose the condition from simple inflammation, in which the results following operation are nearly always most satisfactory.

It is therefore an extremely useful operation in suitable cases, such as obstruction of the common bile-duct from interstitial pancreatitis, and in biliary fistula dependent

on stricture of the common bile-duct, but only rarely is it justifiable to perform the operation in cancer of the head of the pancreas, as, at the best, life in such cases is not considerably prolonged by any operation. It can rarely be justifiable or wise to perform it in gall-stone obstruction, as the modern operation of choledochotomy, which removes the obstruction, can be performed in as short a time and is curative, whereas any short-circuiting operation performed for gall-stones leaves the irritating foreign bodies, which may lead to other complications.

The anastomosis ought unquestionably to be made between the duodenum and gall-bladder, as in that way the secretions mix with the food in the normal position and, the duodenum being part of the intestinal canal less frequented by organisms than the bowel lower down, there is practically little or no danger of infection of the bile-passages. As a matter of fact, we have never seen infection to occur in any case of duodeno-gall-bladder anastomosis, but we know of cases in which an anastomosis between the gall-bladder and colon has been followed after a time by multiple abscesses in the liver and death from pyæmia.

If it should be thought desirable to perform cholecystenterostomy in cancer of the head of the pancreas, it will be desirable to carry out the operation with great expedition, and in such a case it may be justifiable to make the anastomosis to the colon, or, better, to a loop of the jejunum which can be brought up on the right side of the great omentum.

The late von Mikulicz suggested an entero-anastomosis of the jejunal loop, as shown in the diagram (Fig. 140), but this has never been found necessary in our experience, and as it prolongs the operation by a few minutes, we do not think it should be carried out in any patient very seriously ill.

If the adhesions around the duodenum are not too

extensive so that much time would be occupied in detaching them, the operation of cholecystenterostomy may be facilitated by Kocher's method of mobilizing the duode-

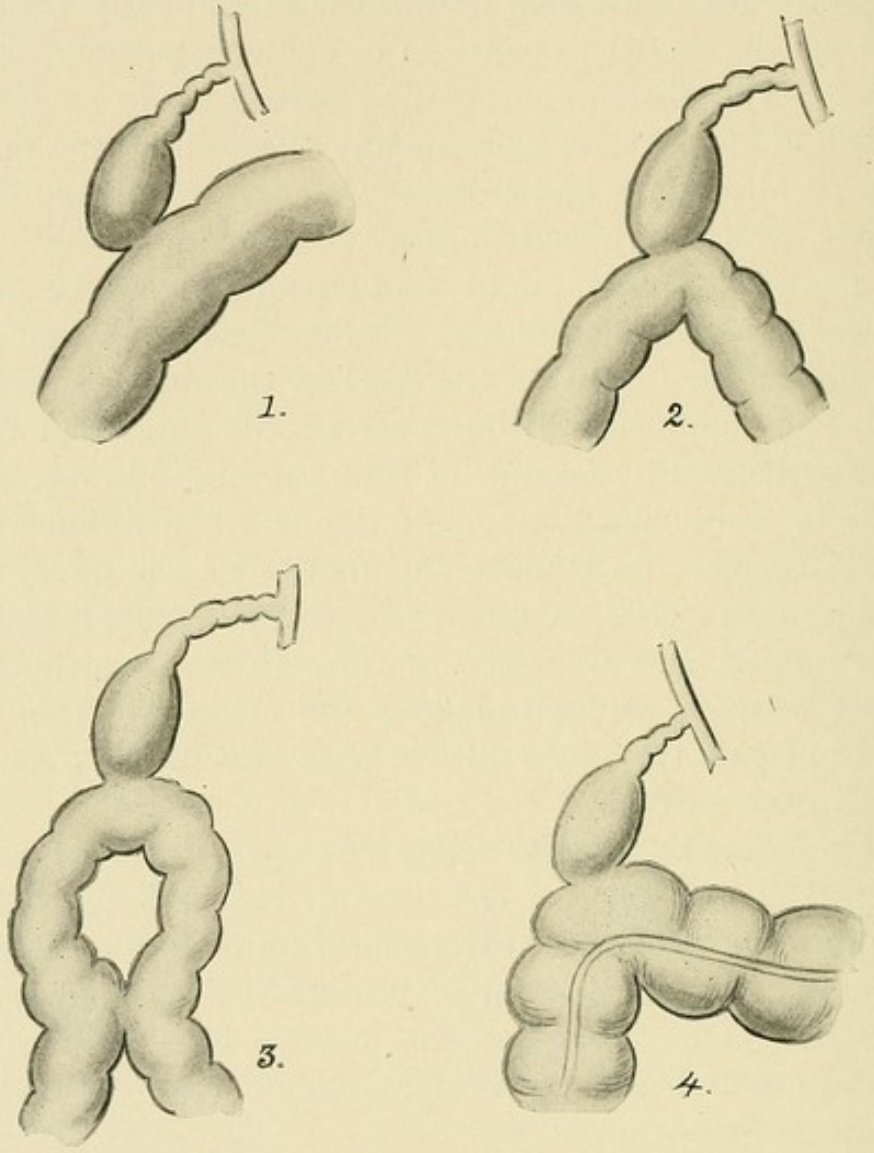


Fig. 140.—1, Anastomosis of gall-bladder with duodenum; 2, anastomosis of gall-bladder with jejunum; 3, anastomosis of gall-bladder with small intestine and lateral anastomosis of intestine; 4, anastomosis of gall-bladder with colon.

num. This is effected by incising the parietal peritoneum of the posterior abdominal wall vertically about an inch to the outer side of the duodenum; by inserting the finger

into this slit, the loose cellular tissue in front of the kidney is easily stripped, and the duodenum can be displaced inwards and, without difficulty, brought forward and clamped before the anastomosis is made, but, as a rule, mobilization of the duodenum is unnecessary if the curved clamps (first invented by Sir Thomas Smith for intestinal work and shown in the diagram, Fig. 141) are applied to the duodenum when the patient's hepatic region is made to bulge forwards, either by the special table we use, or by the sand-bag under the back.

Having grasped the fundus of the gall-bladder and the nearest part of the duodenum separately in clamps, the

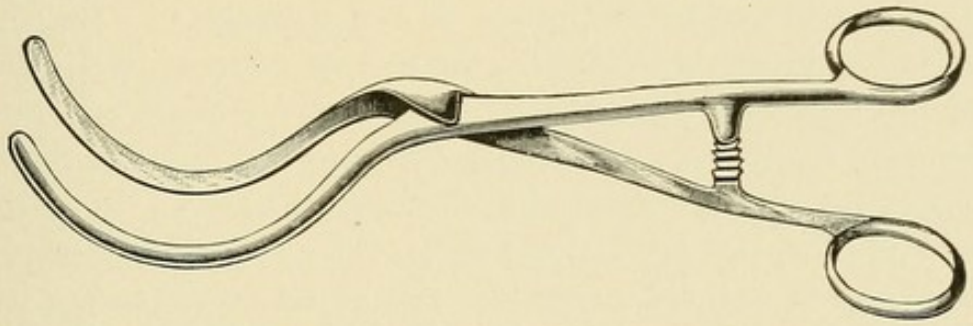


Fig. 141.—Intestinal clamp employed in the operation of cholecystenterostomy.

two viscera are approximated and the serous surfaces united by a suture of fine Pagenstecher's thread for at least an inch, or better 1¼ inches, in length; in front of this the two viscera are incised to the extent of an inch and the margins of the incision in the two viscera are united all around by a fine continuous chromic catgut suture, after which the Pagenstecher suture is continued around the front of the circle outside the marginal suture until it reaches the starting-point, where the two ends are knotted and cut short.

The anastomotic opening is thus secured by a marginal continuous catgut suture, which unites all the coats of the two viscera, and an external continuous suture of

Pagenstecher's thread, which unites the serous and subserous coats external to the marginal sutures.

The junction may be made by a Murphy button, or by a Mayo Robson's decalcified bobbin, but we prefer the method of union by suture, which is both expeditious and effectual.

The advantage of cholecystenterostomy in interstitial pancreatitis is that it provides for permanent drainage of the bile-passages, so that should the inflammatory tissue in the pancreas further contract and cause increased pressure on the bile-duct, no jaundice will occur, and should the inflammatory process in the pancreas take some weeks or months to completely pass away, the patient will not be distressed by the presence of a biliary fistula or inconvenienced by the absence during that time of the bile from the intestines; moreover, there will not be the anxiety of any further operation to face, as there would be after a cholecystotomy. But, besides the relief of jaundice, the operation acts on the pancreas by relieving tension and thus enabling the gland to discharge its contents, which when infected and imprisoned in the ducts, tends to keep up inflammation and to lead after a time to atrophy of the gland substance proper and the formation of fibrous tissue.

It will be gathered from the foregoing arguments that we believe the operation of cholecystenterostomy to be the operation of choice for the treatment of interstitial pancreatitis, and only in case of absence or contraction of the gall-bladder, or in case of unusual difficulties from adhesions or from the serious condition of the patient, would we counsel cholecystotomy being done.

Results.—In considering the after-results of the surgical treatment of the class of cases under consideration it is necessary to give both the immediate risks of operation and the ultimate issue of those cases that recovered. To this end letters were addressed to the friends or medi-

cal attendants of all patients who had not recently been heard of.

Of one hundred and two operations undertaken in patients where chronic pancreatic trouble constituted the chief disease, or where it formed a serious complication of other diseases, 96.1 per cent. of cases were followed by recovery, giving a mortality of 3.9 per cent., but since compiling the foregoing figures, in 1904, our experience has very largely increased, and the mortality has diminished to a little over 2 per cent.

Of the four cases that died, one was a cholecystotomy undertaken in a patient very deeply jaundiced and reduced to the last stage of exhaustion before a surgical opinion was sought, and where at autopsy a cirrhotic condition of the head of the pancreas was found. The second was a cholecystenterostomy undertaken in a deeply jaundiced patient in the presence of extensive adhesions, which, on account of the feeble condition of the subject, seemed too formidable to deal with. In this case a necropsy revealed a calculus in the pancreatic portion of the common bile-duct, occluding the opening of the pancreatic duct, which would have been discovered had the patient's condition permitted a thorough exploration. A third case was in a very feeble patient operated on away from home, extremely jaundiced, and suffering from repeated rigors. Drainage was imperfectly carried out, and she died of cholæmia two weeks later. And a fourth case was a choledochotomy in an aged, feeble man, who died of heart failure, accelerated by intestinal hæmorrhage, in the third week after operation, when the wound had healed.

In the fifty-five cases of catarrhal interstitial pancreatitis where gall-stones were found obstructing the pancreatic portion of the common duct, choledochotomy was performed in forty-two, cholecystotomy in nine, and cholecystenterostomy in four.

Of the fifty-two patients that recovered, forty-eight were living and well when last heard of; one is apparently well nine and a half years subsequent to operation, though sugar has recently been found in his urine; one died from cirrhosis of liver and ascites a year after, it being present and far advanced at the time of operation. Another has since died of acute bronchitis, and another from some other non-specified ailment.

In one case where the cause was pancreatic lithiasis, and where calculi were removed both from Wirsung's and Santorini's ducts, the patient is now in very good health.

In forty-six cases of interstitial pancreatitis without gall-stones or other removable cause, the bile-ducts, and thus indirectly the pancreatic ducts, were drained in nineteen cases by simple cholecystotomy, in seventeen by cholecystenterostomy, and in five by separation of adhesions and thoroughly freeing the ducts. Of the forty-five patients that recovered, no reply to letters was received from six, who were well some time after operation. The rest were in good health when last heard of, with the exception of one (not drained) who has developed glycosuria some years after operation, but is otherwise well; one who shows signs of permanent damage to the pancreas by the urinary test; and one who has anæmia suggestive of the pernicious type.

Besides the nineteen cholecystotomies, were five where the pancreatitis was associated with duodenal ulcer, and in these cases a posterior gastro-enterostomy was performed at the same time, with good results in every case.

It will thus be seen that in a very large percentage of cases the removal of the cause, together with drainage of the bile-ducts, or, in the absence of a removable cause, the simple drainage of the bile-ducts alone, is an operation that may be safely recommended in suitable cases that have failed to yield to general treatment.

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CHAPTER XVII

PANCREOLITHIC CATARRH AND PANCREATIC CALCULI

Pancreatic calculi are exceedingly rare. Two cases were observed by Panarol and Galea in 1667, one by Morgagni in 1765, and Cowley, in 1788, referred to an instance observed by himself. Matthew Baillie, physi-

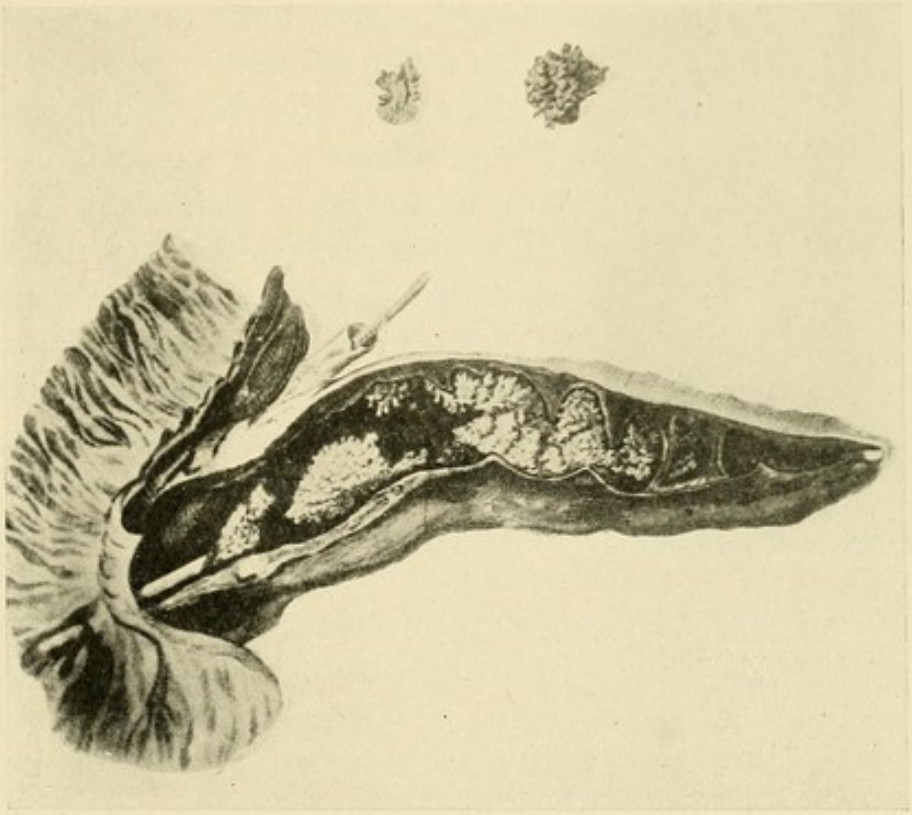

Fig. 142.—Pancreatic lithiasis (Baillie).

cian to St. George's Hospital, in a work on "Morbid Anatomy," published in 1799, figures a case of pancreatic calculi most carefully dissected and showing the relation of the bile-duct and pancreatic duct (Fig. 142).

In 1883 Johnston collected the notes of thirty-five recorded cases. The fullest account was given in 1896 by Guidiceandrea and was based upon forty-eight recorded cases and two observed by the author. Others have since been reported, but they are so uncommon that Oser said there were in 1903 only seventy recorded cases. We have been able to collect others described since that date, and not included in that series, but doubtless there are many unrecorded. The subject of pancreatic concretions can never assume the importance that attaches to cholelithiasis, but as pancreatic calculi are associated with serious and usually progressive disease of the gland, and as they can be removed by operation, their recognition and treatment are matters that demand some consideration.

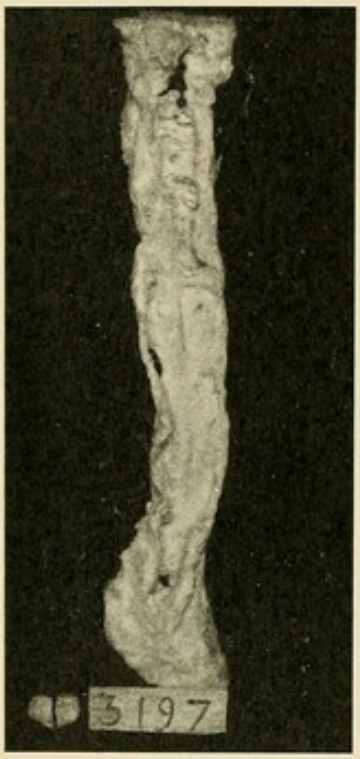

Fig. 143.—Calcification of the duct of Wirsung with atrophy of the pancreas (Univ. Coll. Hosp. Museum, 3197).

Calculi are never found in a healthy pancreas, and it seems highly probable that, like gallstones, pancreatic concretions are the result of catarrh of the ducts with stagnation of secretion, which generally, if not always, results from infection. Instead of calculi being formed, the ducts may actually be lined with calcareous material that may accumulate so much as to close completely, or almost completely, the lumen. An example of this, taken from a specimen in the University College Hospital Museum (Fig. 143), illustrates this condition. It will be noticed that the duct of Wirsung is widely dilated and that it also contains calculi.

An interesting case in which the head of the pancreas

was infiltrated with calcareous material has been reported by Delagénière. The patient was a man of fifty-nine, who complained of violent epigastric pains followed by increasing jaundice. At operation the gall-bladder was found to be distended and to contain a biliary calculus. A resistance was felt in the region of the common duct which was thought to be a large calculus, but, on careful examination, it was found to be a hardening of the head of the pancreas around the common duct. On making an incision into the affected area it was found to be densely infiltrated with small, hard, calcareous granules, 15 grams of which were removed with a curette. The cavity thus formed was drained and the patient eventually made a good recovery, being relieved of his symptoms and able to return to work. Microscopical examination of the material removed at operation showed that it consisted of pancreatic tissue infiltrated with calcium salts which formed hard, yellowish-white granules, mostly of the same size, but in some instances agglomerated to form larger masses.

The composition of pancreatic calculi is important from the diagnostic point of view, for they contain lime, either in the form of carbonate or phosphate, or, as in one case reported by Mr. Shattock, of oxalate, which latter was found in a cyst.

Johnston gives two analyses of pancreatic calculi:

I

Phosphorus salts	72.30
Carbon salts	18.90
Organic matter	8.80

II

Carbon salts	91.65
Magnesium carbonate	4.15
Organic matter	3.00

J. A. Milroy reported as follows on a pancreatic calculus removed by Moynihan: "The stone contains nearly 50 per cent. of calcium carbonate. A small portion of the

solution in which the magnesium was estimated was unfortunately used for qualitative testing, so that I cannot state the exact quantity of magnesium present. These were the only inorganic substances found. I was somewhat surprised to find phosphates absent. The organic substances consisted almost entirely of proteid. Traces of organic substance soluble in alcohol and ether were present. In the residue from the alcoholic and ethereal solutions cholesterin and fat were the only bodies identified. Purin bases and uric acid were absent. The quantity of the original powder was rather too small to allow of an accurate estimation of the constituents."

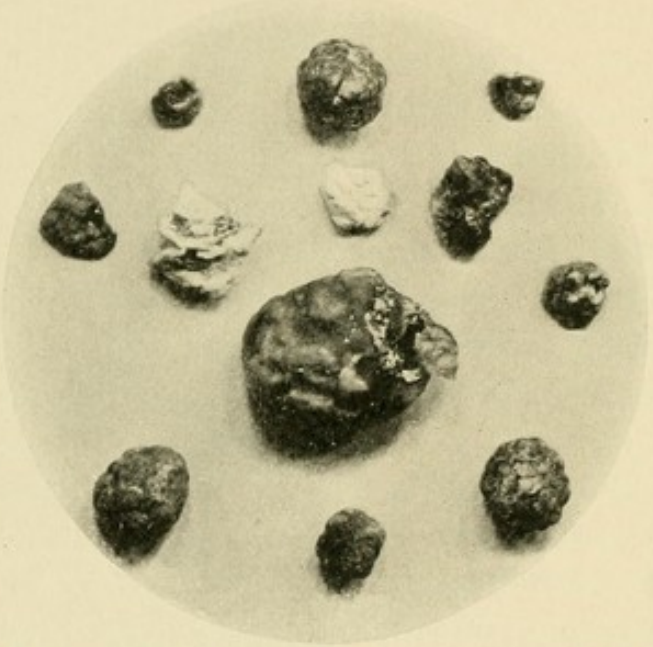

Fig. 144.—Gall-stones and pancreatic calculi.

In examining the urine of cases suffering from chronic pancreatitis, oxalate of lime crystals have been found in over 40 per cent. of our cases. In jaundiced cases in which the bile acids take up the lime salts they have been found only in 6 per cent. of cases. It would be interesting to know if this fact has any bearing on the composition of pancreatic concretions, for it is a well-known fact that the normal pancreatic secretion contains no calcium carbonate. The subject is worthy of further investigation.

The consequence of their chemical composition is that pancreatic calculi are opaque to the *x*-rays, and in this

way we have a means of diagnosing their presence and of differentiating them from gall-stones, which are not seen in a skiagram. An *x*-ray photograph of concretions taken from a case where at the same time gall-stones and pancreatic calculi were removed by one of us is shown in the figure (Fig. 145), and for comparison an ordinary photograph of the two classes of concretions together is also shown (Fig. 144). The difference in their appearance in the skiagram is readily seen. The next photograph,

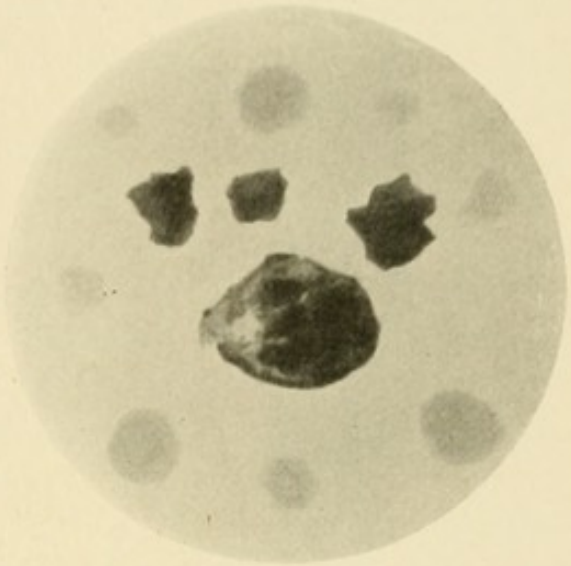

Fig. 145.—*x*-Ray photograph of the pancreatic calculi and gall-stones shown in Fig. 144, showing that the former are opaque to the rays.

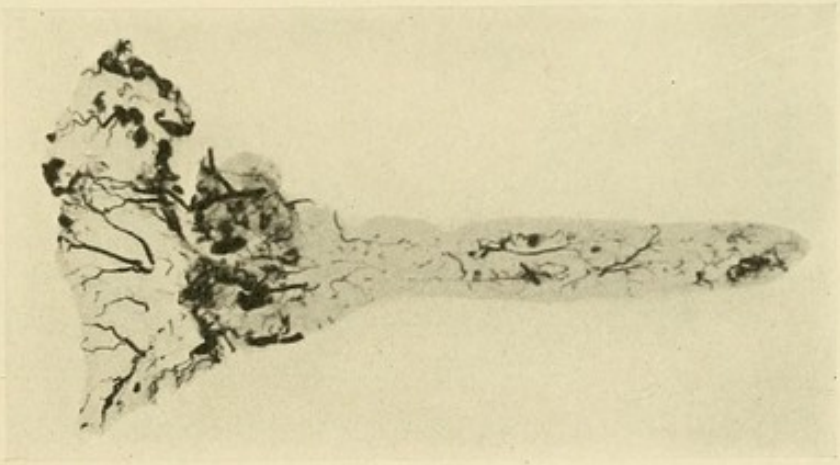

Fig. 146.—Skiagram of pancreas containing calculi; vessels injected.

taken by Dr. J. Mackenzie Davidson, shows the calculi *in situ*, and as the vessels have been injected they also

show distinctly. So far as we are aware, this method of diagnosis was suggested for the first time by one of us in the Hunterian Lectures delivered at the Royal College of Surgeons in March, 1904.

By means of this and the urinary pancreatic reaction it will probably be possible to confirm the diagnosis by demonstrating the associated chronic pancreatitis.

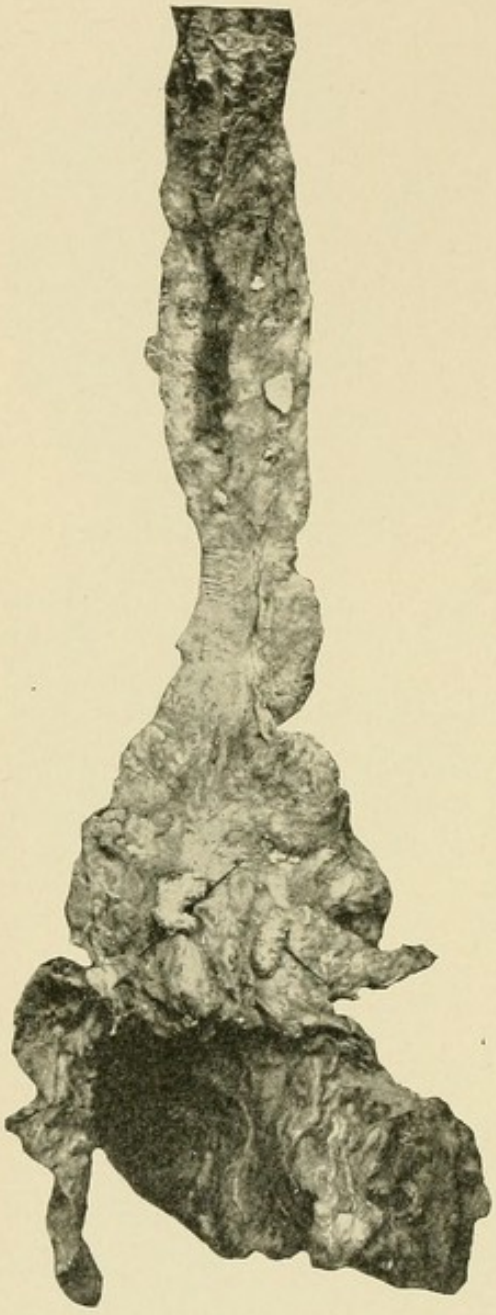

Fig. 147.—A pancreas, with calculi of various sizes in its ducts, which are dilated (Museum R. C. S., specimen No. 2833).

Fig. 148.—Some of the larger calculi from the specimen shown in Fig. 147 (Royal Coll. of Surg. Museum, 2834).

The stones are rounded, ovoid, or elongated like a date-stone. They are found in all parts of the ducts of

the pancreas, though much more frequently in the head; in the tail of the gland they are rarely seen. The calculi may be branched like coral, the trunk of the stone lying in the main ducts and its offshoots in the secondary ducts, but they are usually smooth. Shupmann has recorded a calculus measuring 2½ inches by ½ inch and weighing 200 grains, and Matani has reported one weighing 2 ounces. In colour they are pale and they may be white, but if they pass into the common bile-duct they receive a covering of cholesterin and may be stained by the bile so as to look like gall-stones.

Concretions, consisting chiefly of carbonate of lime, are sometimes found in the pancreatic ducts of cattle. They vary in size from a millet-seed to a hazelnut and are white, cylindrical, angular, or facetted. The duct and its chief tributaries are generally dilated like a string of beads and its walls are thickened.

Symptoms.—The symptoms depend on the associated condition, whether that be cyst, abscess, chronic inflammation, or other pathological state; doubtless in some cases symptoms are vague, or even wanting, and in some cases pancreatic calculi have only been discovered post-mortem. Pains at the epigastrium radiating towards the inferior angle of the left scapula, often agonising in character and associated with vomiting, may be present, and the attacks may be brought on by exertion, or they may be irregular, coming on at any hour, day or night. The pain frequently comes in sharp colicky attacks, similar to, but less severe than, those due to gall-stones. A sense of soreness or stiffness is noticed for a day or two after the attack. When the pain is at its height, vomiting, hiccough, rigors, cold sweats, or collapse may be noticed. After the attack some fragments of stone may be found in the motions (Minnich, Leichtenstern, Kinnicutt). That pancreatic colic is associated with the passage of stones down the ducts seems clearly to be proved by the cases observed

at different times by Minnich and Holzmann, for it was only after each attack that fragments of stone were found in the motions.

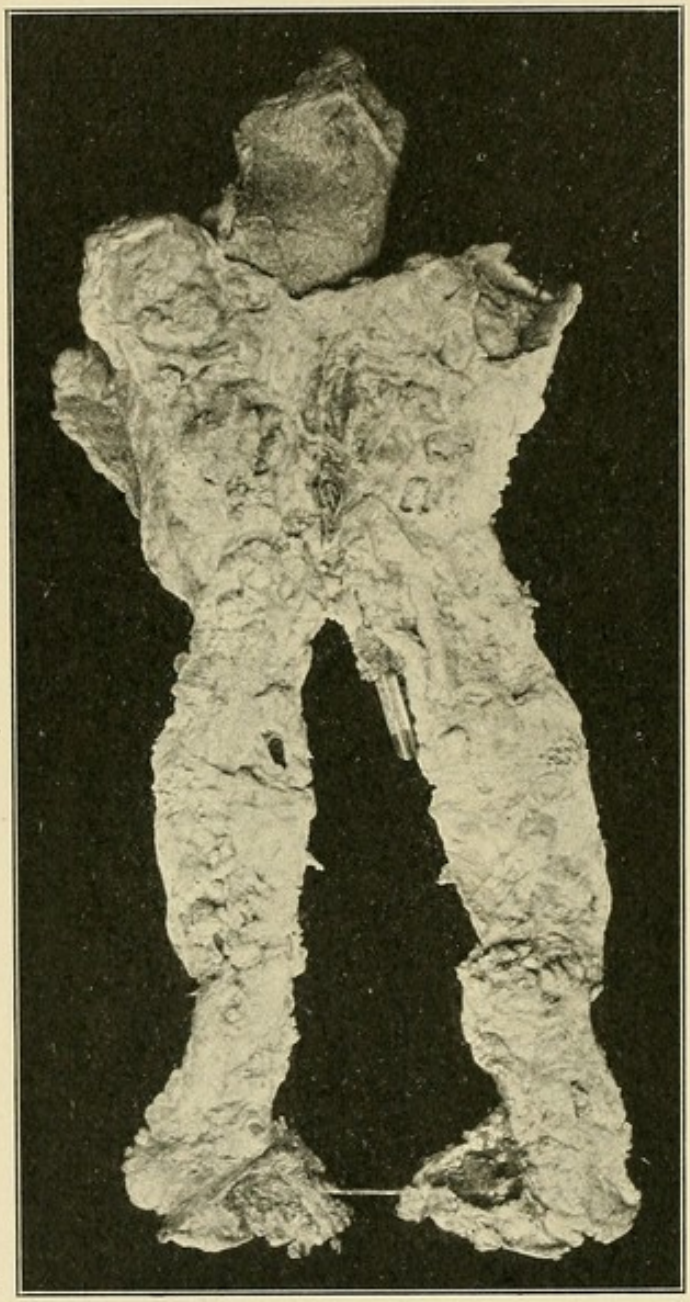

Fig. 149.—Pancreatic lithiasis (Leeds Museum).

Dyspepsia and flatulence are usually present. Liporrhœa and azotorrhœa, as well as bulky pale motions, are present where there is well-marked interstitial pancreatitis, and in some cases where the interstitial changes have advanced to atrophy or fatty degeneration of the whole gland, glycosuria is found.

Glycosuria was recorded by Lancereaux in twelve out of forty cases, but his statement that in each attack of colic there is a temporary glycosuria has not been borne out by the experience of subsequent observers. The presence of sugar may be observed at intervals. Holzmann found it in-

termittently in his case, but while the same patient was under Minnich's observation at an earlier date, no sugar was found, though regularly sought. Caparelli records the case of a woman who developed, after many attacks of acute epigastric colic, an abscess above the umbilicus. The abscess burst and discharged some pus and gritty material. Through the fistula, which persisted for six years, many small stones, over one hundred in all, were expelled. After the spontaneous closure of the fistula, diabetes developed and the patient died.

The pancreatic reaction in the urine was well marked in a case operated on by one of us, to be referred to subsequently, and it will probably be generally found. If a calculus descends into the ampulla of Vater, jaundice will ensue and the case will probably be diagnosed as one of gall-stones in the common duct, but the pancreatic reaction and the use of the *x*-rays should enable a differential diagnosis to be made.

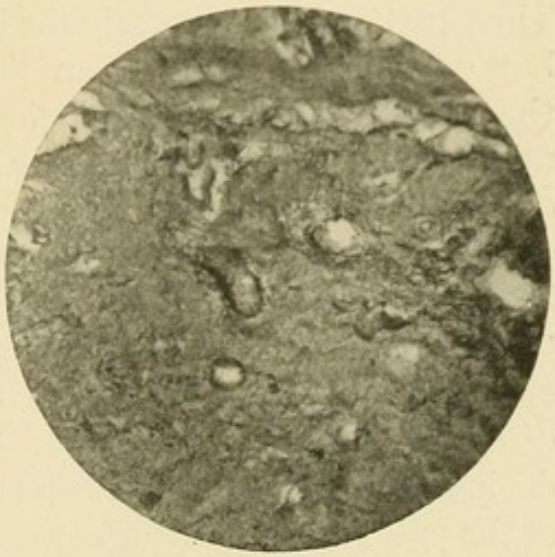

Fig. 150.—Section of the fibrosed pancreas in a case of pancreatic lithiasis (× ca 40).

In a case recorded by Körte a patient suffered from biliary colic for which the abdomen was opened. A large calculus was removed from the gall-bladder, which was drained. While the bile was still discharging the patient experienced an attack of pain similar to that for which operation had been undertaken. After death a tumour in the head of the pancreas, which during life had been

diagnosed as malignant, was found to be an abscess with large concretions in it.

Kümmell records an almost exactly similar case in which cholecystotomy had been performed; pain recurred, and at the necropsy a large soft calculus was found in the canal of Wirsung. Kinnicutt reports an interesting case in a woman, aged forty-two, who had had three attacks of sudden severe pain, beginning in the back and running around the right side along the lower intercostal spaces, with nausea and vomiting. After an interval of eight months, another extremely severe attack occurred. The pain began, as before, in the back between the scapulæ, but on this occasion it ran *through*—not around—into the epigastrium, and became localised to the right of the middle line. On the sixth day after the commencement of the attack six small stones, the size of a pea, were passed per rectum. Four of these were analysed and found to be composed of carbonate and phosphate of lime with no trace of cholesterin or bile-pigment, thus indicating their origin in the pancreatic ducts. Similar stones, or detritus of similar composition, were recovered from the stools during more than one subsequent attack of colic. Some of the patient's later attacks were associated with jaundice and on one occasion two typical gall-stones were recovered from the stools. This case, the author points out, shows the difficulty there is in distinguishing between the presence of biliary and pancreatic calculi. There is nothing distinctive in the nausea, vomiting, diarrhœa, character of pain, or jaundice. The points which are helpful are an *x*-ray photograph, the finding of the calculus and its analysis, glycosuria, and a deficient splitting of ingested fats into fatty acids and soaps. In the case described fat-absorption was normal, but of the fat recovered from the fæces 42.6 per cent. was in the form of neutral fat.

Treatment.—According to the results of the experimental work of Kühne and Lea, the subcutaneous in-

jection of pilocarpine incites the flow of the pancreatic juice but the treatment of pancreatic calculi by sialagogues is probably useless and mere waste of time, although in a case reported from Eichhorst's clinic of "undoubted pancreatic lithiasis," in which subcutaneous injections of pilocarpine were tried, "the attacks of colic disappeared completely and the patient was better than for many months before."

Relief to pain may be given by sedatives, and other treatment must be adopted as occasion arises, but as soon as pancreatic stones can be diagnosed, they should be removed, as destruction of the pancreas is otherwise certain, and it is quite clear that medical treatment can do no real good in these cases.

Surgical treatment has until quite recently been merely palliative, but fortunately surgery can now offer a reasonable hope of cure. The pancreatic duct can be readily explored by an incision in the second part of the duodenum, and by then laying open the biliary papilla the opening of Wirsung's duct can be seen. From this a probe can be passed two inches along the duct to explore it, and by this method we have removed a pancreatic calculus from the duodenal end of the duct.

A very exhaustive search through English and foreign literature has only resulted in the discovery of five operations for pancreatic calculi. Mr. A. Pearce Gould's case, operated on March 3, 1896, died on the twelfth day from exhaustion. In Dr. Dalziel's case a stone of the size of a very large pea was removed from the pancreatic duct through an incision in the duodenum, the opening in the duct being stitched to the wound in the posterior wall of the duodenum. As the bile-duct was clear there was no jaundice. A good recovery followed. In Mr. B. G. A. Moynihan's case a pancreatic stone was removed from the ampulla of Vater through an incision in the duodenum and the patient recovered. In Dr. L. W. Allen's case two

calculi were removed from a cyst between the lesser curvature of the stomach and the liver. The patient died on the fifth day after operation.

In a case which came under the care of one of us on February 13, 1903, four calculi were removed from a woman aged fifty-seven, one from the duct of Santorini, or one of its branches, by direct incision into the pancreas close to the common duct, afterwards closing the opening by deep and by peritoneal sutures; the second and third stones were reached through an incision in the duodenum by laying open the papilla, when by means of fine forceps a calculus was removed out of Wirsung's duct, along which a probe was afterwards passed for two inches, and a fourth concretion was removed by direct pancreatotomy from the middle of the duct of Wirsung, the stone being reached by incising the gastro-hepatic omentum, drawing the stomach downwards, incising the pancreas freely, and opening the duct directly on to the stone, which was of the size of a small bean. The duct was then closed with catgut, the wound in the body of the pancreas being sutured so as to leave no dead space and the peritoneal wounds being closed without direct drainage. The right kidney pouch was then drained, as some infected bile had escaped. Recovery was ultimately complete. In this case pain and vomiting were marked features

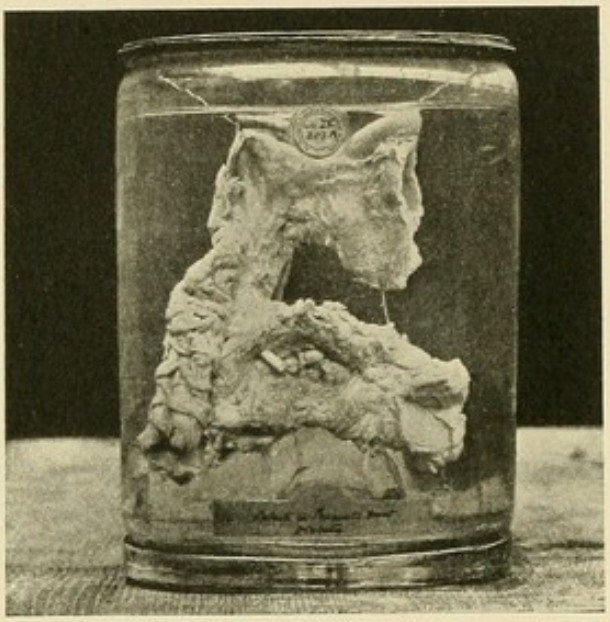

Fig. 151.—Pancreas showing calculi in the duct of Wirsung (St. George's Hosp. Museum, 203).

and the pancreatic reaction was of the utmost importance from the point of view of diagnosis. This is, apparently, the first case in which either the duct of Wirsung or the duct of Santorini has been deliberately opened, and, after the removal of a calculus, closed by a suture.

The Operation of Pancreo-lithotomy.—For the purpose of removing calculi from the pancreas an incision 3 or 3½ inches to the right of the middle line will be found the most convenient, as the fibres of the right rectus can be split and the incision lengthened upwards and downwards without unnecessarily weakening the abdominal wall. A sand-bag under the lumbar spine will bring the gland several inches nearer the surface. If the opening of the duct of Wirsung has to be explored, the second part of the duodenum may be incised and the papilla common to the bile-duct and pancreatic duct laid open, when the edges of the opened diverticulum of Vater can be seized with small catch forceps and drawn to the surface; a probe or fine forceps can then be readily passed into Wirsung's duct and any concretion removed. If the calculi are more deeply placed in the ducts, the pancreas may be exposed either through the gastro-hepatic omentum by drawing the stomach downwards, or by lifting the stomach it may be reached through a slit in the omentum or by raising the colon, by a slit in the transverse mesocolon; or by peeling the duodenum from the parietes the back of the pancreas may be readily reached. The calculi may be then cut down on and extracted by a scoop or forceps. Any bleeding must be arrested by ligatures. The duct can be sutured and the incision in the gland must be brought together by buried sutures, the peritoneal covering being coapted by a continuous suture. If leakage is feared a gauze drain may be applied, but the position may be difficult for this, and if it has to be done the gauze must be surrounded by a rubber drainage-tube and brought through it to the surface. In the case of

pancreo-lithotomy above referred to the closure of the gland was so secure as not to require gauze packing, and the result justified its not being used. When the duodenum is opened it must be closed in the usual way by a muco-muscular and serous suture, the latter being of fine celluloid thread. The incised papilla need not be sutured. If a calculus be felt in the head of the gland, but not in the duct of Wirsung, it may be reached by incising the peritoneum over the duodenum and separating it gently from the head of the pancreas, or if more deeply placed near the back of the gland the reflection of peritoneum from the duodenum to the abdominal wall may be incised and the duodenum may then be displaced inwards, when the back of the pancreas will be exposed, and, if thought advisable, it may be incised and treated as in the incision from the front.

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CHAPTER XVIII

PANCREATIC CYSTS

Although cysts of the pancreas cannot be said to be of frequent occurrence, they have to be taken into account in the diagnosis of any cystic tumour in the abdomen; for, as will be seen later, they may appear in various regions and may simulate many other diseases.

A search through the literature reveals the fact that, excluding thirteen cases in our own experience, one hundred and sixty cases of operation for pancreatic cysts have been recorded. Although larger numbers have been reported in various works, the above figure is probably as nearly correct as possible; for on verifying the records, the same case had sometimes been reported twice, and, in many, the details were so meagre that the nature of the operation was not even given. Dr. Hale White has recorded the fact that in nearly six thousand post-mortem examinations at Guy's Hospital from 1883 to 1894, pancreatic cysts were only found in four cases, and one of these was a hydatid cyst.

Cysts of the pancreas may be divided into false and true. The false or pseudo-cysts may be due to a distension of the lesser peritoneal sac, or to a localised collection of fluid in the neighbourhood of the pancreas.

Seeing that simple drainage is usually sufficient to bring about relief or cure of the disease, surgery offers a poor opportunity for pathological intervention, since experience has shown that the patient's interests are best considered by a limitation of the incision to a size sufficient to empty and drain the cyst, and not sufficiently large to satisfy pathological investigation; hence it is

highly probable that many reported cases of operation for pancreatic cysts have been for cysts of other organs, and it is an undoubted fact that quite a number of the cysts supposed to originate from the pancreas are pseudo-cysts.

True cysts may be due to retention from various causes, to parasitic disease,—*e. g.*, hydatids,—to new-growths, as in proliferation cysts, and to hæmorrhage. A few cases of congenital cystic disease have been recorded.

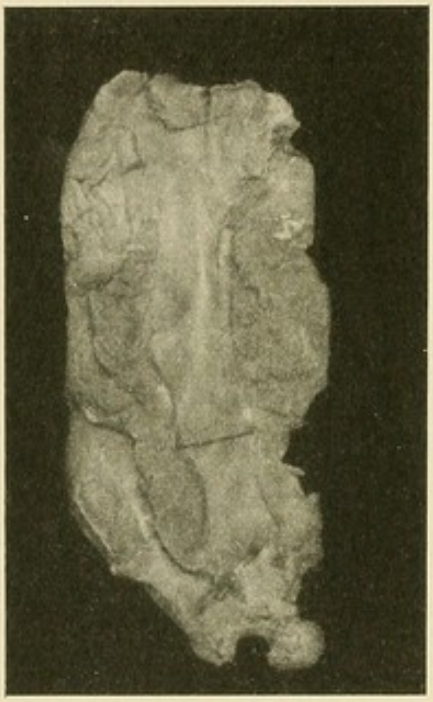


Fig. 152.—Calcification of the orifice of the duct of Wirsung and dilatation of the duct (Univ. Coll. Museum, 3196).

The greater number of chronic cases that come under the care of the surgeon are due to retention of the gland secretion, the outflow of which is hindered in some way.

Senn found that ligature of the pancreatic duct did not result in the formation of a cyst, though chronic or intermittent obstruction might result in cyst-formation; just as ligature of a ureter, or acute obstruction, leads to atrophy of the kidney, though chronic obstruction or an obstruction of an intermittent character tends to the development of hydronephrosis.

The outflow of secretion in the pancreas may be hindered in different ways by obstruction of the excretory duct, or by a combination of compression from without and obstruction from within. The most frequent cause is probably chronic interstitial pancreatitis, in which compression and constriction of the ducts result from the development and contraction of connective tissue, thus leading to stagnation of the secretion. Wirsung's duct

may be closed by gradual compression, as, for instance, in the development of a tumour along its course, or by the gradual development of a duodenal tumour, or a stricture due to ulceration, which compresses the orifice of the duct. Pressure by swollen lymphatic glands, or by adhesions near the head of the pancreas, or even by a gall-stone or Wirsung's duct, may lead to stagnation of secretion, and thus to cystic development.

Occasionally a cyst of the pancreas may result from chronic pancreatitis due to ulceration extending into the pancreas from a chronic ulcer of the posterior wall of the stomach, as in a case which was treated successfully by gastro-enterostomy, and at the same time drainage of the cyst, by one of us.

Large cysts may also be caused by obstruction within the duct, as, for instance, by a pancreatic calculus or by a gall-stone in the ampulla of Vater.

Doubtless some cysts are altogether independent of obstruction and cannot be accounted for by any of these explanations.

A particularly interesting case has been reported by McPhedran, in which a pseudo-cyst and a true cyst were observed in the same individual:

"G. A. B., male, aged fifty-three, in 1891 had an attack of biliary colic, with well-marked jaundice and pale motions. Had two or three similar attacks every year. Condition became gradually worse and there was almost constantly some epigastric discomfort, indigestion, and flatulence. One severe attack of pain lasted three days. The epigastrium was tender and pain radiated in several directions. Was losing flesh. On examination there was a thickening to be felt on deep pressure in the epigastrium. Three days later a large, smooth, cyst-like tumour was found in the epigastrium, extending from the right para-sternal line to the left mammary line and down to the umbilicus. The upper boundary was ill defined. The stomach resonance was above and to the left. A cystic

collection in the bursa omentalis was diagnosed and the abdomen opened. The cyst was emptied. At the bottom lay the pancreas, irregularly enlarged and firm, but somewhat elastic. The peritoneum over it was smooth and healthy looking. There was no sign of hæmorrhage anywhere. Five months later a tumour was again found in the epigastrium. It extended down to the level of the anterior superior spinous process, and laterally to the mammary line on the right, and the anterior axillary line on the left. It forced the diaphragm upwards, so that the cardiac impulse was in the fourth intercostal space. The abdomen was again opened and a cyst exposed lying behind the stomach. The cyst wall was about 2 mm. thick. The fluid was opaque, whitish, and contained many flocculi and masses of fibrin. It was alkaline in reaction, and contained albumin, but no digestive ferment. After drainage the cavity contracted rapidly, but a fistula persisted, and the discharge from this irritated the skin. On examination it was found to possess marked action on albuminoids, fats, and starches, leaving no doubt as to the presence of pancreatic secretion. The condition causing the repeated attacks of colic lay in the pancreas, and may have been a calculus or a localised inflammatory deposit causing mechanical obstruction. In the most acute attacks the symptoms were those of acute pancreatitis."

The **symptoms** produced by a pancreatic cyst vary according to the cause, as well as from the size and the seat of the tumour. They are at first dependent on the disease which leads to the cystic formation, though later the pressure exercised by the tumour itself on the neighbouring viscera has to be taken into account. Seeing that cystic disease is generally associated with some pancreatitis, either local or general, we may expect to find digestive disturbance with loss of flesh and pain at the pit of the stomach quite early in the disease, preceding by some time the recognition of the cyst at the surface. If the cause be dependent on some obstruction in the duct, we may expect to find paroxysmal pains accompanied by vomiting and followed by jaundice and wasting.

If the interstitial pancreatitis is at all extensive, there will be marked loss of flesh associated with fatty stools, azotorrhœa, and bulky, pale motions, and rarely the presence of glucose in the urine. In all the cases of pancreatic cyst that we have recently observed there has been a well-marked pancreatic reaction in the urine, indicating catarrh of the pancreatic ducts, or interstitial inflammation.

The Röntgen rays may also form a useful help in diag-

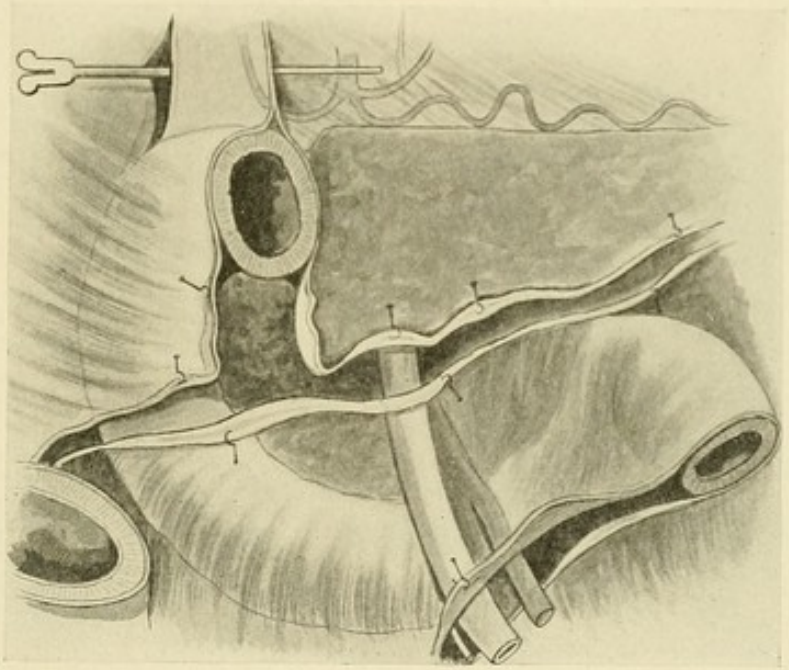


Fig. 153.—Diagram to show the relations of the peritoneal reflections of the pancreas (Testut).

nosis in certain cases, as they may establish the presence or absence of pancreatic calculi.

It is to be borne in mind that there have been cases of pancreatic cyst, presenting very few symptoms except the presence of a tumour, which have been under observation for a long time and have needed no active treatment, but these cases are exceptional. On the other hand, the tumour may be associated with severe pain and distress and with marked digestive and metabolic symptoms.

The physical signs of cysts of the pancreas are by no means constant. A consideration of the peritoneal reflections from the pancreas on to the viscera, and how they influence the ultimate position and relations of pancreatic cysts, will render the reason for this clear (Fig. 153). For instance, a tumour may spring from the anterior surface of the head or body of the pancreas above the stomach, between it and the liver, or, between it and the transverse mesocolon. On the state of distension of the stomach will depend the extent of contact of the tumour with the abdominal wall. By distending the stomach with air through a tube, or by giving doses of soda and tartaric acid in separate draughts, the relation of the stomach to the cyst can be readily shown. If a cystic tumour arise from the pancreas to the right of the omental bursal reflection, it may make its way forwards to the right hypochondrium and simulate a gall-bladder or right renal or suprarenal cyst. Should a cyst arise from the posterior part of the head or tail of the gland, it may project either into the right or left lumbar region and resemble a cyst of the kidney. If a tumour springs from the head of the pancreas below the reflection of the transverse mesocolon, but to the right of the mesenteric vessels, it will reach the surface below the hepatic flexure of the colon on the right side, and may simulate a right renal tumour, or a tumour of the cæcum, or ascending

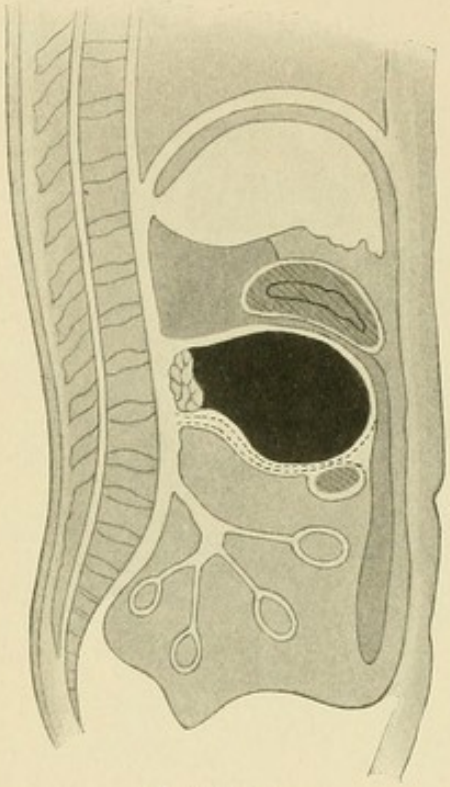


Fig. 154.

(Figs. 154 to 158 are a series of diagrams to show the directions in which pancreatic cysts may develop.)

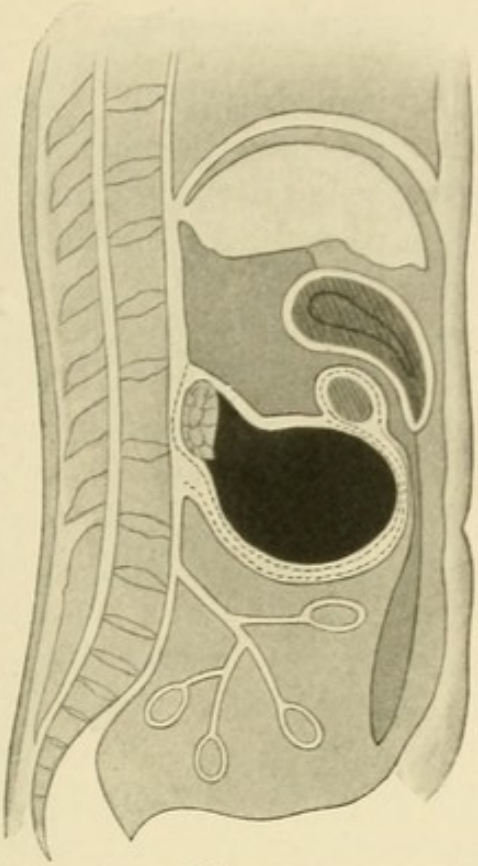


Fig. 155.

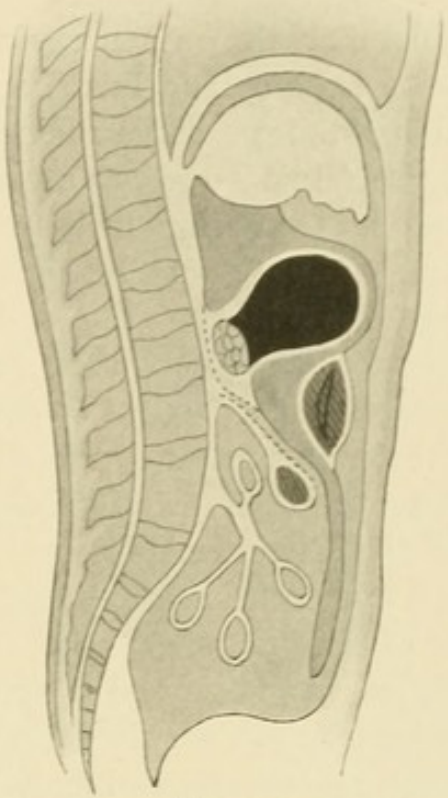


Fig. 157.

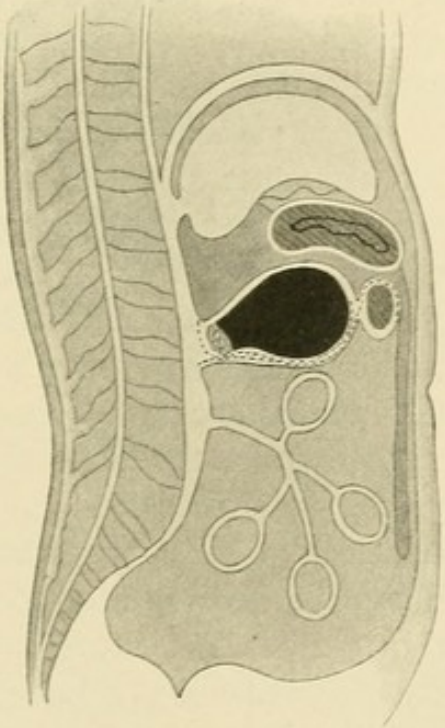


Fig. 156.

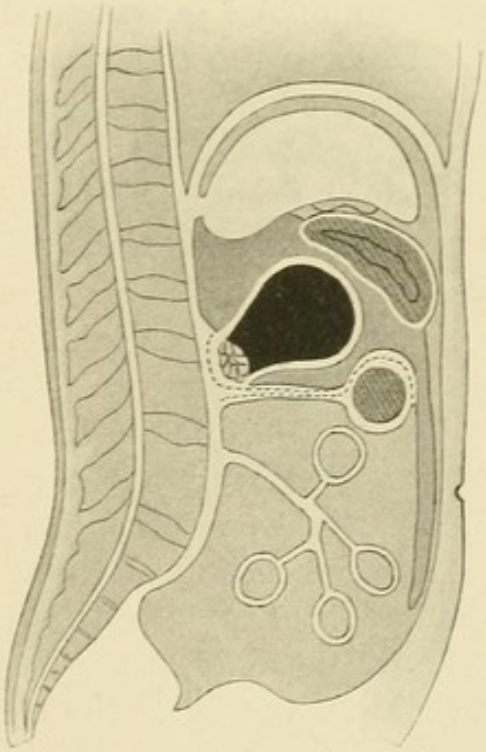
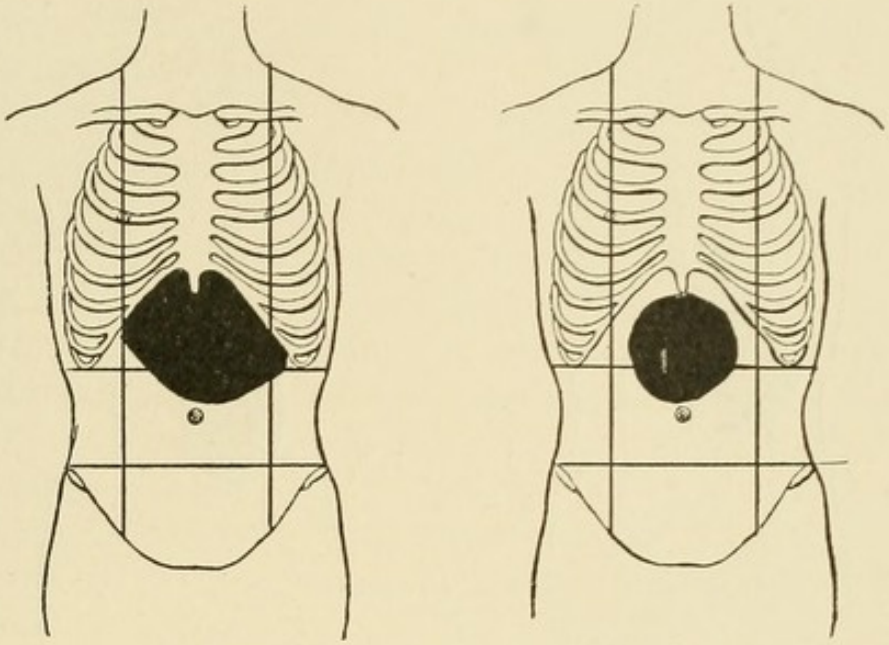


Fig. 158.

colon, as the mesentery will prevent it passing to the left of the spine; but should it arise from the small portion of the processus uncinatus on the left of the mesenteric vessels, but below the attachment of the transverse mesocolon, it may burrow between the layers of the mesentery and simulate a mesenteric cyst, or it may bulge on the left of the mesentery and reach the surface below the transverse colon on the left of the spine, when it may resemble a left renal or ovarian cyst, or a tumour of the descending colon, or small intestine. A tumour arising from the body or tail of the pancreas above the reflection of the transverse mesocolon will pass upwards beneath the left costal margin, and resemble a cyst of the spleen, or of the left lobe of the liver. A pancreatic cyst in this region may be opened and drained under the idea that it is a cyst of the spleen, and a chronic abscess of the spleen may, on the other hand, be opened and drained under the idea that it is a cyst of the pancreas.

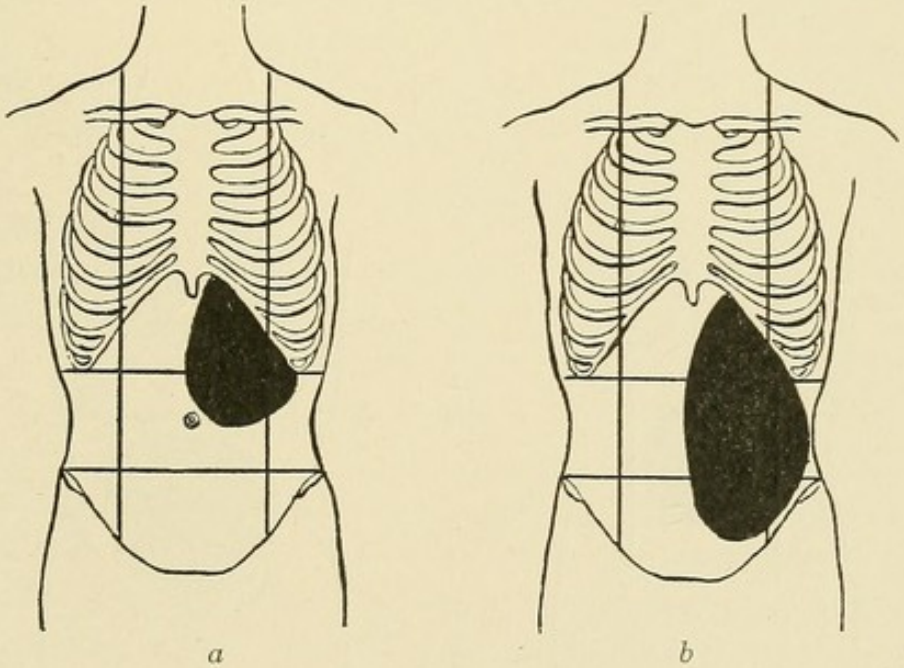
Tumours springing from the pancreas on the left of the duodeno-jejunal junction, where the lower surface of the gland lies on the transverse mesocolon, have a tendency to press the great omentum forward and to project above the transverse colon, but they may grow downwards towards the central region of the abdomen and arch the transverse colon, or even project below it, so that the colon lies above the tumour. The relationship of the colon to the cyst may be ascertained by distending the colon with air introduced *per anum*. In an interesting case recorded by Dr. S. P. Phillips a thin-walled pancreatic cyst springing from the head of the pancreas completely filled the abdomen and presented the physical signs of ascites.

The explanation of these variations, which may, and often do, lead to difficulties in diagnosis, is an anatomical one, and depends on the site of origin of the cyst, which in making its way to the surface proceeds in the line of least resistance, and is thus influenced by the reflections



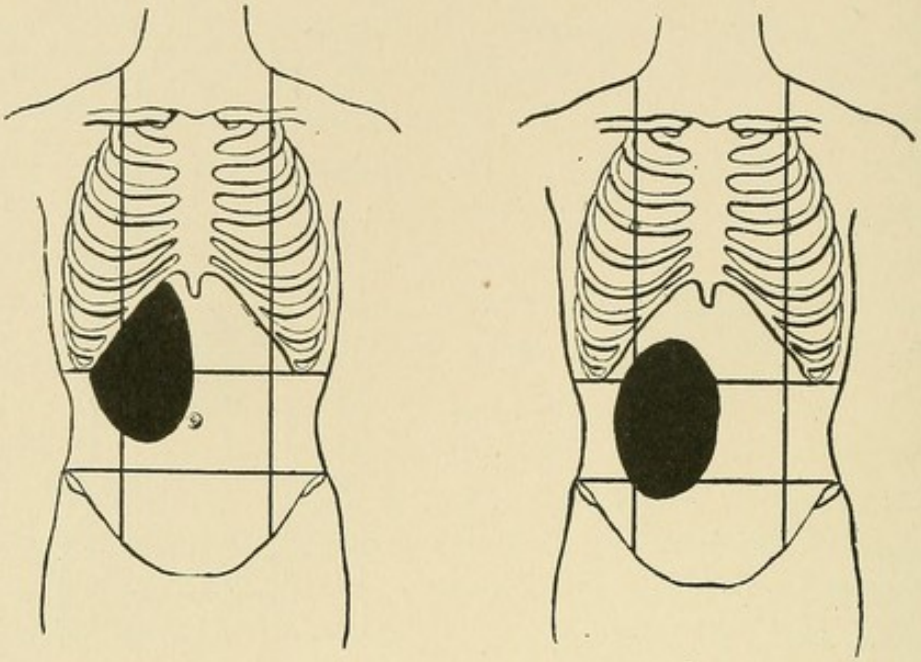
a *b*

Fig. 159.—*a*, Traumatic pancreatic effusion into the lesser peritoneal sac, in a boy æt. two years, knocked down by a cab; *b*, cyst of pancreas treated by incision and drainage, man æt. thirty-five years; well seven years later.



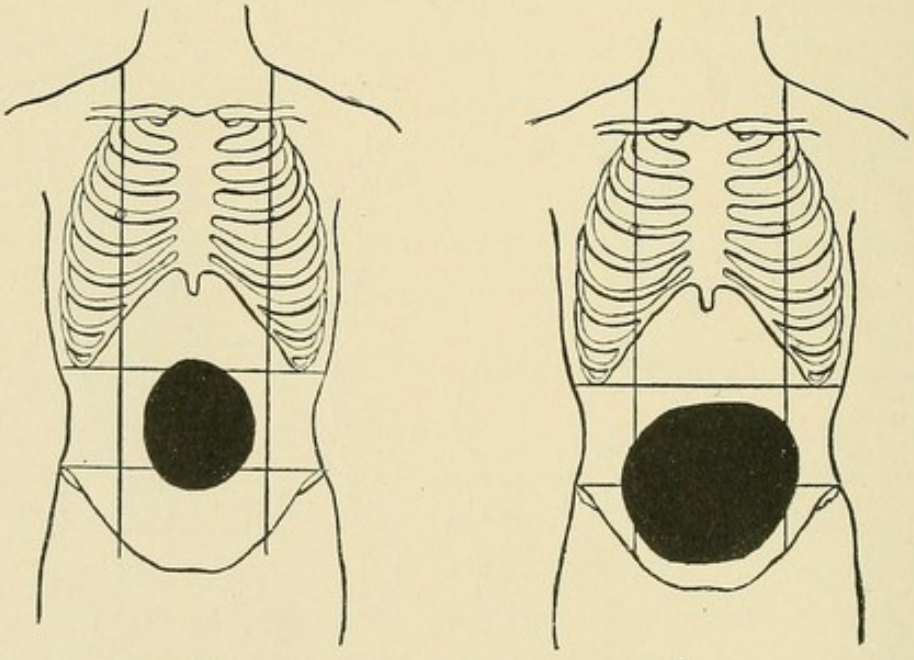
a *b*

Fig. 160.—*a*, Cyst of tail of pancreas treated by incision and drainage; cure. *b*, Cyst of pancreas from man æt. thirty-seven years; drainage, recovery.



a *b*

Fig. 161.—*a*, Pseudo-cyst of pancreas formed around necrosed pancreas in a man æt. fifty-eight years. Patient in good health two years later. *b*, Cyst of pancreas treated by drainage; man æt. fifty-three years; short fistula remains, otherwise well.



a *b*

Fig. 162.—*a*, Cyst of body of pancreas; drainage; recovery. *b*, Pancreatic cyst resembling ovarian tumour.

of the peritoneum and the arrangement of the viscera overlying the gland.

Diagnosis.—A cyst of the pancreas may thus simulate a dilated and tense gall-bladder, a cyst of the liver, spleen, or kidney, an omental or mesenteric cyst, an ovarian or uterine cyst, a cystic dilatation of the bile-duct, a suprarenal cyst, a tubercular peritonitis, or even an ascites. It is evident, therefore, that the presence of a cystic tumour alone, even in a characteristic position, will not justify the diagnosis of cyst of the pancreas, though, as a rule, the combination of symptoms together with the physical signs should leave little doubt in the majority of cases as to the nature of a tumour, even before an exploration of the abdomen is done. It used to be a favourite diagnostic method to explore by a hollow needle any cystic tumour; but it can be only under very exceptional circumstances that this aid to diagnosis would be justifiable, as it is by no means devoid of danger from perforation of an overlying viscus (*e. g.*, stomach, colon, etc.), or perforation of a large vessel or extravasation of the cyst contents. Not only so, but the examination of the contents will not always make the diagnosis certain. If, however, such an exploration be decided on, it is better to employ a small aspirator needle, and at the same time to completely empty the cyst, which, if tense, would otherwise be liable to leak into the peritoneal cavity, and produce disastrous consequences. While it is easy to say what will be the physical signs on

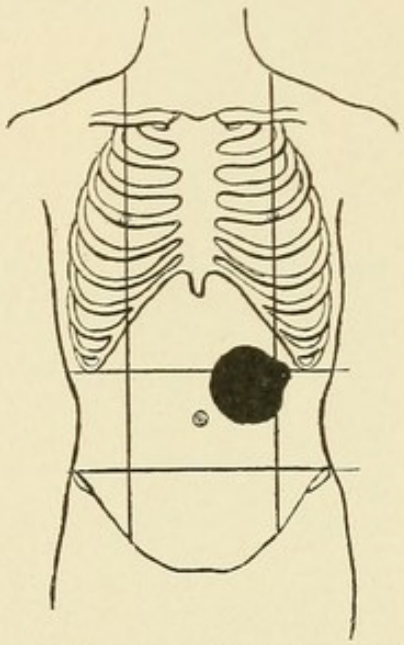


Fig. 163.—Cyst of tail of pancreas, from a woman æt. thirty-eight years; drainage; recovery. Recurrence; excision of cyst; recovery.

percussion and palpation of a cyst appearing above, behind, or below the stomach, or above, behind, or below the transverse colon, it will be seen that no one description can in any way guide the surgeon as to the regular signs to be found in a pancreatic cyst reaching the surface.

Fig. 164.—Dilatation of the duct of Wirsung (Royal Coll. of Surg. Museum, 2832 A).

The shape of a cyst varies according to the way in which it originates from Wirsung's duct, or from the smaller canals within the gland. Thus there may be a rosary-like dilatation of the whole duct, as in a photograph taken from a specimen in the College of Surgeons' Museum, shown in the illustration (Fig. 164). Virchow termed this "ranula pancreatica," from its analogy to the well-known cystic tumour in the mouth.

If several small ducts are constricted, the resulting cysts may be small and multiple, especially if associated with diffuse chronic pancreatitis (Fig. 165). In case of partial cystic-dilatation of Wirsung's duct, large cysts may form which may be oval or rounded and may vary from the size of a fist to enormous sacs containing as much as 20 to 30 pints of fluid, though the ordinary size of pancreatic cysts is something between that of an orange and a child's head.

The thickness of the cyst wall will vary according to the amount of pancreatic tissue entering into its structure, but in some cases it may be quite thin. It should

not be forgotten that large blood-vessels may be encoun-

Fig. 165.—Pancreas showing small retention cysts (Leeds Medical School Museum, E E 203).

tered in the walls of the cyst. The lining of the cyst is generally smooth, but in some cases it may be roughened and show ridges and septa the remains of several original cysts; or there may be found, adherent to the inner surface of the cyst, clotted remains of profuse hæmorrhages. The contents of a cyst may resemble water, and may give the appearance of a hydronephrosis having been tapped, or the fluid may be thick and slimy. More frequently, however, the contents of the cyst are light brown, or coffee-ground, in colour. The fluid may also be syrup-like and gelatinous, or colloid or purulent. In some cases it may be yellowish-green, as if mixed with bile.

Fig. 166.—Retention cyst of the tail of the pancreas (St. George's Hosp. Museum, 202 A).

It will thus be seen that the naked-eye appearances of the contents of the cyst do not always form a guide as to its true nature. A chemical analysis of the fluid often affords positive assistance. The fluid from a pancreatic cyst is alkaline in reaction, and generally of low specific gravity, 1.010 to 1.020, although Gussenbauer in one case found a specific gravity of 1.160. The amount of solid matter is not high; thus, Herter analysed the contents of two pancreatic cysts and gives the following results of three examinations:

	I	II	III
Total solids	24.1%	24.1%	23.8%
Organic matter	17.9%	14.9%	18.5%
Ash	6.2%	9.2%	8.7%

Albumin is always present, and, occasionally, mucin also. Traces of urea have been noted in some instances, and cholesterin is frequently found. A very complete analysis of the contents of a pancreatic cyst has been recorded by Alay and Rispal. In their case the following results were obtained: Reaction feebly alkaline, albumin 8.9 grams per mille (serum albumin 5.2 grams per mille, globulin 0.6 gram per mille, albumose 3.0 grams per mille, peptone *nil*), urea 0.14 gram per mille, uric acid traces, fat and cholesterin 0.16 gram per mille, sugar *nil*, acetone about 0.05 gram per mille, chlorides 5.8 grams per mille, phosphates 0.16 gram per mille, sulphate traces, calcium and magnesium 0.05 gram per mille. The ash contained iron and traces of copper.

Microscopically blood cells are usually found. There may be epithelial cells, fat globules, and cholesterin crystals.

The most important characteristic, however, is the possession by the fluid of digestive powers resembling those of pancreatic juice. When it is found to readily digest albumin, starch, and fat, there can be no doubt as to the nature of the cyst from which it is derived, but the exact value of the discovery of one or other of the ferments alone is still a matter of dispute. Körte considers

that a powerful starch-converting ferment is of great diagnostic value, and it is no doubt very suggestive, but it must be remembered that von Jaksch has shown that the fluid from various abdominal cysts, and even from cases of ascites, has distinct starch-converting powers, so that it is now generally acknowledged that the presence of a diastatic ferment alone is of little value in diagnosis. According to Boas, the presence of an albumin-digesting ferment is most characteristic, but in many cases of undoubted pancreatic cyst this has been absent, especially in old encapsuled cysts. Its absence in more recently formed cysts is explicable by the fluid not having been activated by the enterokinase of the succus entericus, while its presence in other cases may be due to the action of soluble calcium salts, etc., which, according to Delezenne and Wohlgemuth, have a similar effect to enterokinase. Since the fat-splitting power of pancreatic juice is its most characteristic property, it might be expected that the possession of this power by a fluid will at once decide its origin, and, according to our own observations and those of Zeehuisen, this is, in fact, the case. Unfortunately this question has not been gone into in many cases, but as the methods of examination now available are comparatively simple, it is to be hoped that a larger body of evidence will shortly be available.

With regard to the results of an examination for ferments, it may be said that the presence of all the enzymes in considerable amounts points to a cyst arising from, or directly connected with, the pancreas, while their absence is of no value one way or the other. The presence of a starch-converting ferment alone is of little value in diagnosis, but the proteolytic and fat-splitting ferments are important, and afford presumptive evidence of a cyst of pancreatic origin. The presence of the ferments does not necessarily mean that the fluid is contained in a true pancreatic cyst, however, for they may be found in pseudo-

cysts arising from injury or laceration of the pancreas. In such cases the ferments are furnished by the pancreatic secretion finding its way through the injured or torn peritoneum into the lesser sac, where they mingle with the inflammatory exudate forming the bulk of the fluid. The digestive powers of a fluid of this description are not so well marked as those seen in a typical pancreatic cyst, but they may be equally as active as those met with in true cysts of some standing, in which the surrounding pancreatic substance has been replaced by fibrous tissue from the associated inflammatory changes.

The **termination** of pancreatic cysts, in the absence of treatment, varies in different cases. There is usually a steady progress of the disease that has caused the cystic condition—as, for instance, in the case of interstitial pancreatitis towards atrophy, and its consequence, diabetes; but pressure symptoms may produce danger before this slower termination, or the cyst may rupture into the peritoneal cavity and cause death by shock or by peritonitis. Rupture into the stomach or intestine has also been known to occur.

In some cases pancreatic cysts have existed for many years without producing any serious symptoms, though this is exceptional.

Treatment.—It is quite clear that medical treatment can be of no avail in the case of pancreatic cysts, and that surgical treatment alone is available for relief or cure.

Aspiration and other forms of tapping are inadequate and ineffectual methods, which are attended with more danger than is the operation of incision and drainage. They are, therefore, not to be recommended, even for diagnostic purposes. Occasionally complete extirpation of the cyst may be performed, as in a case that came under the care of one of us, where the tumour returned a few months after it had been apparently successfully treated by drainage; but the greater difficulty in performing

excision, its impracticability in certain cases and the greater mortality attending it, as compared with the operation of incision and drainage, make it quite clear that drainage should always have a fair trial unless the circumstances prove to be very exceptional, as, for instance, in the case of a cyst of the tail of the pancreas, or in the case of a pedunculated cyst.

As to the situation for drainage, that will depend on circumstances. The tumour will usually be attacked most readily from the front at a point where it very nearly reaches the surface. Occasionally, however, it may be drained from the loin.

Fistula does not, as a rule, follow the drainage of pancreatic cysts, but in some cases a small fistula may persist and may go on for years without hurt to the patient and with very little discomfort.

The following is a description of the operation usually performed: An incision is made through the parietes opposite the most prominent part of the cyst. When the peritoneum is opened, the finger can be employed to ascertain the relations of the cyst and its attachments. If the stomach is in front of the cyst, it will be better to displace that viscus upwards and to make a slit through the great omentum in order to expose the cyst wall; if the colon is in front, it may be displaced downwards. But no rule can be formulated, as the cyst must be reached in the most convenient way, and that can be ascertained only when the abdomen is open. By means of an aspirator the fluid is then drawn off, and an opening made in the cyst sufficiently large to allow of a drainage-tube being inserted. The tube may then be fixed to the margin of the incision in the cyst by a single catgut suture, and if the opening into the cyst is surrounded by a purse-string suture, which can be tightened around the tube, all fear of leakage from the cyst into the peritoneal cavity is avoided. Any vessels coursing over the cyst must be

avoided, but should an artery or vein be pricked, it must be caught between pressure forceps and ligatured.

The edge of the cyst may then be fixed to the aponeurosis by three or four sutures, but it is better not to attach it to the skin. The abdomen is then closed, and if the tube is sufficiently long it will readily drain into a bottle containing some antiseptic fluid. If, on exploration, the cyst is found to have a narrow attachment to the pancreas and the adhesions are not too extensive, it may possibly be shelled out, or the pedicle may be ligatured, but this is rarely feasible.

Some surgeons have suggested the desirability of fixing the cyst to the surface and only opening it after a few days, when adhesions have formed, but this operation *à deux temps* seems to be quite unnecessary.

Statistics.—In the cases that have come under our personal observation, one cyst was enucleated, recovery following; drainage was carried out in ten cases of true cyst, recovery following in nine; whereas of two pseudocysts, one due to traumatic hæmorrhagic pancreatitis and the other to necrotic pancreatitis, one recovered.

Of the one hundred and sixty cases of operation recorded by others, there were one hundred and forty recoveries; in four cases the ultimate issue was doubtful; in eight out of the one hundred and forty reported recoveries after operation the patients died subsequently—one from diabetes four months later, one from hæmorrhage one-and-a-half years later, one from concomitant peritonitis seven weeks later, one from a zymotic fever a few weeks later, and three from causes not stated, a few weeks later. Death is recorded as the result of operation in twenty cases. In five of these the cause of death and the time after operation are not given. One patient died in collapse, one died before operation could be completed (the next day), one died from "ileus," one died eighteen days after operation (cause not stated), two died from

shock, one died from gangrene of the pancreas, and eight died from peritonitis; one died at an interval not stated, one after ninety-six hours, one after six days, one after an exploratory incision, two after two days, one on the eighth day, and one on the second day. In one hundred and thirty-eight cases incision and drainage were performed, with sixteen deaths, equal to a mortality of 11.6 per cent. In fifteen excision was performed, with three deaths, equal to a mortality of 20 per cent. In seven partial excision was done, with one death, equal to a mortality of 14.3 per cent.

Although larger numbers have been reported by others, the above figures are as nearly correct as possible, for on verifying the records sometimes the same case had been reported twice, in others wrong dates had been given, and in a few the details were so meagre that the nature of the operation was not given. The evidence is clearly in favour of drainage, but the mortality should certainly be reduced by one-half.

PROLIFERATION CYSTS

Many of these tumours are on the border-line between cystic carcinoma and proliferating cystomata, and it is only the subsequent course of events that indicates to which class they belong.

The *cystic epitheliomata*, or *carcinomata*, are cystic formations, generally multilocular, with cancerous deposits in their walls. There are usually secondary deposits of growth in the liver or adjoining structures. Only very few cases have been reported, and the presence of metastatic growths generally renders them inoperable.

The *cystadenomata* or *cystic simple tumours*, although more common than the malignant variety, are yet uncommon. Cumston, writing in the "Annals of Surgery" for February, 1903, was only able to find reports of fifteen cases. They are almost always multilocular, lined with

cylindrical epithelium, and form crypts, or polypoid masses, projecting into the cavity of the cyst. They are more common in the tail than the head of the gland. Since their contents are frequently blood-stained, some observers have considered that they are of hæmorrhagic origin and have referred to them as "apoplectic cysts." Others believe that they are formed by the fusion of minute cysts resulting from obstruction of the small excretory ducts following interstitial inflammation. In support of this view it has been pointed out that no evidence of a proteolytic ferment could be found, and that it was possibly used up in digesting the walls separating adjacent cysts. The proteolytic ferment is not, however, always absent, and it is sometimes the starch or fat-splitting ferment that has been lacking.

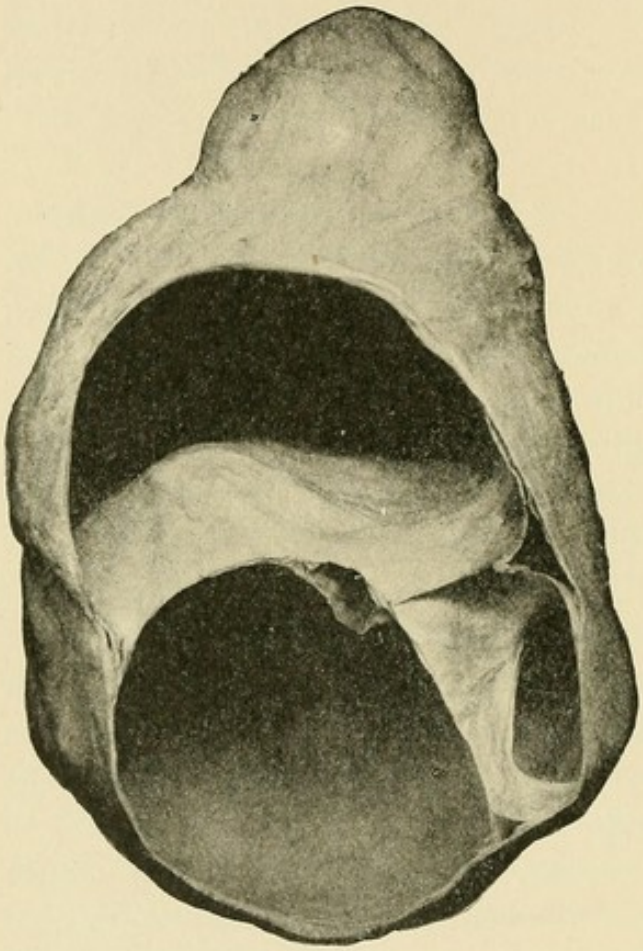


Fig. 167.—Thin-walled cyst of the pancreas (Royal Coll. of Surg. Museum, 2834 A).

A case in which a multilocular cystic tumour of the pancreas was removed with good results, has recently been reported by Mr. J. D. Malcolm, and is the second in which this surgeon has operated.

The patient, a female, aged fifty, felt something move in her abdomen and was very sick about six months before she sought medical advice. This disturbance soon passed off and she "forgot" about the "lump," but she began to lose flesh and strength about that time. A month before she fainted, and was very pale for the following week. The fæces were "like ink" for three days and then resumed their natural colour. Apparently there had been a hæmorrhage into the upper part of the alimentary

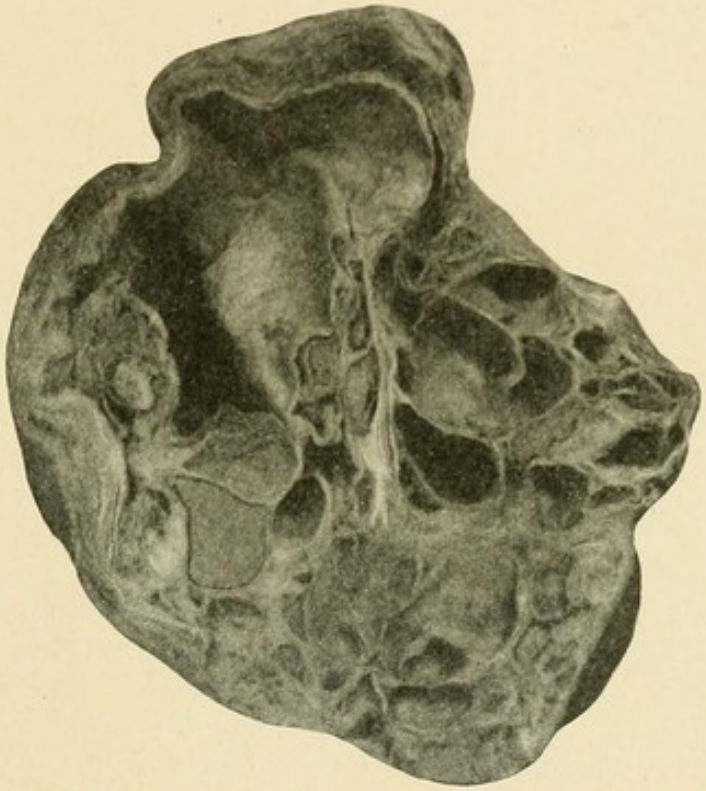


Fig. 168.—Multilocular cystic tumour of the pancreas (Royal College of Surgeons Museum, A 2835).

tract. The patient again became conscious of something abnormal in her abdomen. Her general condition was good, the urine was normal, and the bowels acted well without medicine. There was an oval, hard tumour in the left side of the upper abdomen measuring about 4 inches in its lateral diameter and rather more from above downwards. It had considerable mobility, exactly resembling that of a large loose kidney, the greatest fixity being towards the spine. The percussion note over the most

prominent parts was dull before and behind, the area of dulness varying with the position of the tumour. The right kidney was somewhat mobile. A malignant growth in a loose left kidney, the capsule of which had not yet ruptured, was diagnosed.

At the Samaritan Free Hospital, on April 26, 1905, the abdominal cavity was opened by an incision outside the left rectus muscle. The transverse colon was seen to be displaced downwards and pressed forwards by a growth between it and the stomach. There was only one layer of serous membrane over the tumour, which apparently had developed to the left of the lesser sac of the peritoneum. The kidney was in normal position behind the neoplasm and the tail of the pancreas lay across the upper inch, or rather more, of its anterior surface, intimately attached to it. Many vessels over the tumour were ligatured as they were divided, and the mass was gradually freed without much loss of blood until its only attachment was to the pancreas. This gland was cut into so as to get the whole growth away. The pancreatic tissue bled freely, but it showed no friability, and ligatures applied to it held well. A large vein, quite a third of an inch in diameter, was cut across and there was a profuse hæmorrhage for a moment, but both ends were secured with forceps and safely tied. When the pancreas was released it immediately turned round so that its anterior aspect presented unharmed. Evidently the new-growth had arisen from the posterior surface of the gland, and rather from the upper part of it. The fact that the pancreas had been incised gave rise to no subsequent trouble. In enucleating the tumour both layers of the transverse mesocolon were divided and the edges of the inferior layer were brought together by sutures. A drainage-tube was inserted through an incision below the twelfth rib, the anterior abdominal wound was closed, and healing gave no trouble.

From the first there was considerable distress caused by vomiting and retention of flatus. The bowels acted when enemata were given, but every attempt to give the patient a sufficient quantity of food was followed by symptoms of a partial obstruction of the bowel, and there was an increasing tendency to intestinal distension. A

great deal of peristaltic movement became visible in the epigastric and umbilical regions and down almost to the pubes. It was thought that the small intestine was adherent somewhere, probably to the wound of the transverse mesocolon, and as the patient was losing ground the abdomen was reopened on the sixteenth day after the operation. It was then obvious that the large intestine was at fault and that the difficulty was caused by an unusually acute angle at the splenic flexure, the mobility of the transverse colon being interfered with by adhesions between it and the anterior abdominal wall. The ascending and transverse colons were elongated, distended, and tortuous, so as to fill the area where peristalsis had been visible. The adhesions were released, a lateral anastomosis was made between the transverse and descending colons, and flatus escaped freely from the rectum a few hours after the operation. There was for a time a tendency for fæces to collect in the colon, but there were no further urgent symptoms, and the patient, who had become very emaciated, gradually put on flesh and left the hospital on July 3. She was seen again on March 13, 1906, when her general health was good and the bowels were acting regularly without medicine. She complained of a dragging pain in the right side, and the left kidney was much more mobile than it had been, but a belt and pad gave relief.

The tumour was a multilocular cystoma measuring about 4 inches by about $3\frac{1}{2}$ inches, with a small amount of solid tissue here and there between the cysts. It is preserved in the museum of the Royal College of Surgeons of England.

Congenital cystic disease of the pancreas is exceedingly rare. In a work on the pancreas by Mayo Robson and Moynihan reference is made to three cases, and we have been unable to meet with a record of any other instance subsequent to these. The condition resembles that met with in other organs, with which it has been associated in at least one case.

Hæmorrhagic Cysts.—Many pancreatic cysts contain a considerable quantity of blood, and it has been sought

to distinguish between "hæmatomata," or retention cysts into which blood has escaped, and "apoplectic cysts," resulting from hæmorrhage into softened gland substance. Although it is not impossible that a blood-containing cyst may arise in either way, there is no certain criterion by which they can be distinguished, and even if it were possible, the distinction would merely be of theoretical interest and of no practical value. The arguments bearing on the question have already been discussed in the chapter on pathology.

Hydatid cysts of the pancreas are extremely rare, and present no surgical peculiarities calling for special mention. They must be treated by drainage and evacuation of the daughter cysts, and on no account must incision of the cyst be attempted, though in some cases it may be possible to completely evacuate the endo-cyst and thus to expedite recovery.

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CHAPTER XIX

NEOPLASMS

Tumours of the pancreas are far from common and are usually of a malignant nature. Among the lower animals, according to Nocard and Friedberger, new-growths of the gland are especially common in dogs and are usually of a carcinomatous or adenomatous type.

Carcinoma.—Carcinoma is no doubt the most common of the neoplasms found in the pancreas, but until recently it has not figured prominently in the text-books, the reason probably being, as Dr. Sidney Phillips has pointed out, that the secondary nodules which form in the liver during the course of most cases of cancer of the pancreas are so much more readily recognisable both during life and at post-mortem examination than a nodule of cancer in the pancreas, which requires to be searched for, that many cases of cancer of the pancreas have been considered as examples of cancer of the liver. This is borne out by the fact that since more attention has been directed to diseases of the pancreas, the deaths certified from cancer of the organ have risen, while the deaths certified as from cancer of the liver have fallen in number. Thus the deaths certified to the Registrar-General from cancer of the pancreas increased year by year from 281 in 1899 to 436 in 1904, the most marked rise being from 340 in 1903 to 436 in 1904, while in the same twelve months the deaths registered from cancer of the liver and bile-ducts fell from 3901 to 3736. No doubt many cases of cancer of the pancreas still escape registration as such.

Out of 53,000 necropsies gathered from various sources, where post-mortem examinations were presumably care-

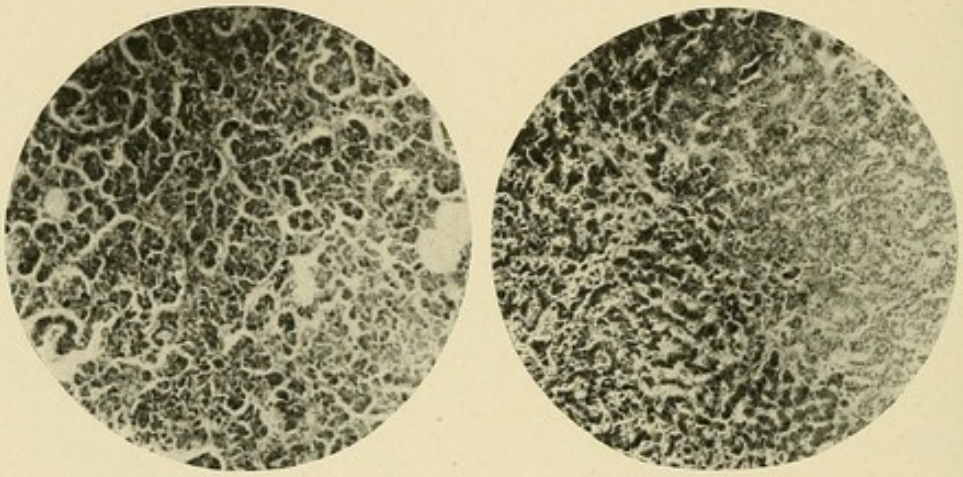
fully made, there were 226 cases of primary malignant disease of the pancreas (Roswell Park), but as these include Remo Segre's cases from the Ospedale Maggiore, Milan, in which the primary and secondary growths are not separated, the proportion of primary growths is probably not so large. Secondary growths are much more common; for instance, in Eppinger's statistics, of 1314 necropsies there were 308 cancers in various organs, of which 19 were in the pancreas, but of these only 2 were primary. It seems advisable to remark here that all past post-mortem records with regard to cancer of the pancreas must be fallacious, as until the appearance of our paper on chronic pancreatitis in July, 1900, cases of chronic interstitial pancreatitis causing occlusion of the common bile-duct were not differentiated.

Fig. 169.—Primary columnar-celled carcinoma of the pancreas (×50).

The tumour in cancer may take the form of scirrhus or encephaloid cancer, columnar celled carcinoma, or colloid cancer, and these are given in their order of frequency. Secondary deposits may be found in any situation, but are most common in the liver. In Fig. 170 is shown a metastatic deposit in the liver secondary to cancer of the pancreas, showing how the secondary disease conforms to the type of the primary.

Cancer usually occurs after forty years of age, though we have met with a case of cancer of the head of the pancreas at thirty-two years of age, and rarely it has been known to occur in childhood.

Symptoms.—The first symptoms are loss of weight and strength with indigestion and general malaise, pain being usually absent or unimportant. When the head of the pancreas is involved jaundice rapidly ensues, the skin assumes a dark almost black colour, unlike the yellow colour of jaundice from gall-stones, the liver swells, and the gall-bladder dilates. The patient then seems almost to dissolve away, the loss of flesh being so rapid. The motions become pale and contain fat and muscle fibre, if meat be taken. Chemical analysis of



a *b*

Fig. 170.—*a*, Primary spheroidal-celled carcinoma of the pancreas; *b*, edge of a metastatic deposit in the liver, from the same case, growth to the right, liver to the left (× 42).

the stools shows that there is not only a large excess of unabsorbed fat, but that the "neutral fat" is much increased relative to the "combined fatty acid," owing to the absence of the fat-splitting ferment of the pancreatic juice from the intestine. In cancer of the head of the pancreas obstruction of the common bile-duct is, as a rule, absolute at an early stage, and consequently the fæces contain no stercobilin. The urine gives no "pancreatic" reaction by the improved or "C-method" in most cases, but in some the attendant inflammatory changes cause a more or less marked deposit of crystals. By the

original "A-reaction" large, slowly soluble crystals may be secured in most instances, but in some no reaction is obtained, and in others it may be necessary to examine several specimens of urine, and to make more than one preparation from each, before they can be obtained. In interpreting the results of the "pancreatic" reaction in the urine it is important that these points should be borne in mind, and particularly that by the C-reaction a deposit of crystals due to a pancreatitis, associated with the spread of the growth, may be present in some 25 per cent. of cases (see table, page 225), or otherwise they may lead to an error in diagnosis. Sugar is found in the urine only when the whole gland is involved in the growth, or when by secondary interstitial pancreatitis both the secreting parenchyma and the islands of Langerhans have been destroyed. It is therefore not commonly met with.

There is, as a rule, no difficulty in diagnosing cancer of the head of the pancreas from chronic interstitial pancreatitis, for, apart from the usual difference in the results of the pancreatic reaction, the general symptoms, especially the duration and mode of onset of the disease, as well as the information obtained by a complete and thorough chemical and microscopical examination of the fæces, will usually enable the diagnosis to be made. In exceptional cases, especially when the tumour is large and growing rapidly, pain may be severe and excruciating, and, if the stomach is involved, vomiting assumes a prominent place. In some instances an analysis of a test meal for free and physiologically active hydrochloric acid may afford useful confirmatory evidence in suspected cases of cancer, but although their absence may be taken as supporting a diagnosis based upon other grounds, their presence, even in considerable amounts, cannot be depended upon as indicating the simple nature of a tumour. The hæmorrhagic tendency in connection with cancer of

the head of the pancreas and jaundice is well known, but even in cancer of the body or tail of the organ a hæmorrhagic condition may ensue. Probably the excretion of lime salts from the blood may account for the hæmorrhagic condition and for the relief that can be given by the use of calcium chloride. Bleeding from the stomach or from the nose and mouth, and from the intestine, or hæmorrhages under the skin are apt to occur spontaneously, and to become serious, or even fatal, and in case of operation, unless the blood be previously charged with lime salts, bleeding is likely to occur in the shape of persistent oozing, both at the time of operating and subsequently.

When the tumour attains any size, it may be palpated from the front, but in ordinary scirrhus of the head of the pancreas no tumour can be felt, except enlargement of the gall-bladder, which is generally present. Occasionally, however, there may be no marked enlargement of the gall-bladder until late in the case, either from the cystic or hepatic duct being gripped by the growth, or no enlargement throughout, from absence of the viscus, as in the case reported by Stewart, or its almost complete obliteration from previous inflammatory changes. Bronzing of the skin may come on if the adrenals are involved. Ascites or dropsy of the lower limbs may follow from pressure on the portal vein or inferior vena cava, or from secondary involvement of the liver, but apart from pressure, slight œdema of the feet is often an early sign. Death occurs from exhaustion, as a rule, within a few months, and is never very long delayed; in fact, cancer affecting the head of the pancreas is more rapidly fatal than when occurring in any other organ. The typical clinical picture of malignant disease of the pancreas may thus be drawn: A patient suffers for a time from indefinite symptoms of digestive disturbance, then jaundice appears, coming gradually, but persistently increasing; the gall-bladder is usually distended and the liver is normal

or slightly enlarged at first and greatly enlarged later. A tumour may be found in the neighbourhood of the pancreas. Cachexia rapidly develops, and, in some rare cases, pain disturbs the patient's rest. There is soon a feeling of intense prostration and weakness. The fæces are massive and contain fat, the normal relation between the "neutral fat" and "combined fatty acids" is disturbed, and an undue proportion of undigested muscle fibre is

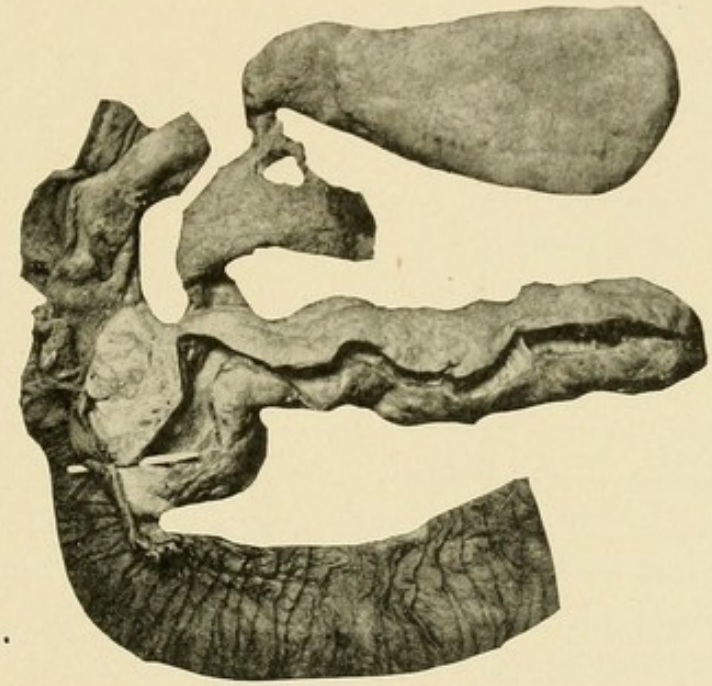


Fig. 171.—Carcinoma of the head of the pancreas causing dilatation of the pancreatic duct, common bile-duct, and gall-bladder (St. Thomas' Hosp. Museum, 1414).

present in the stools. The urine contains albumin frequently, and sugar and fat rarely. The whole clinical course is run, as a rule, within twelve months, and after the appearance of jaundice within from six to eight months.

Differential Diagnosis.—In malignant disease of the pancreas the symptoms are not constant. The cases may be divided into three chief types: (1) Where the tumour extends to the right and compresses or occludes the common bile-duct and the pancreatic ducts. (2)

Where it takes an upward and forward direction and, besides compressing the bile-duct, leads to pyloric stenosis. In this case, to the typical symptoms are added those of dilated stomach. (3) Where the extension is backwards, causing compression of the vena cava, and of the portal veins, thus leading to an early onset of ascites and later to œdema of the lower extremities. When the body and tail of the pancreas are involved the symptoms are atypical, and the development of a tumour with steady loss of strength and increasing anæmia are such as might be due to any malignant tumour outside the pancreas. In the differential diagnosis of cancer of the head of the pancreas we must consider common-duct cholelithiasis, interstitial pancreatitis, cancer of the common bile-duct, cancer of the liver, cancer of the pylorus, and chronic catarrh of the bile-ducts. Whenever, in a patient at or past middle age, jaundice comes on painlessly and becomes absolute, at the same time that the gall-bladder gradually enlarges so as to form a perceptible tumour, and the patient rapidly loses flesh and strength, a diagnosis of cancer of the head of the pancreas will probably be correct. The diagnosis will be made more certain if there is an absence of tenderness below the right costal margin, associated with a tumour opposite to, or above, the umbilicus, having communicated pulsation and not moving with respiration. On distending the stomach with air or carbonic acid gas it will be found that the tumour, at the best rather indefinite, becomes hidden behind the resonant stomach, and that the distended gall-bladder becomes pushed to the right. If cholelithiasis has preceded the onset of cancer, the gall-bladder will not be enlarged, but the rapid deterioration of health and the presence of anasarca and ascites will, as a rule, leave no doubt of the nature of the disease.

In common-duct cholelithiasis there is always a preliminary history of gall-stone attacks, though it may

have been years previously. The jaundice will have come on after pain and is probably never absolute, for some bile nearly always escapes past gall-stones in the common duct. The bile soon becomes infected, and ague-like seizures follow, with an irregular temperature, at times almost resembling pyæmia. In place of a distended gall-bladder a rigid right rectus will be felt, which often makes it difficult to examine the parts beneath. A tender spot will usually be found an inch above, and to the right of, the umbilicus, and the pain will be found to pass backwards to the midscapular region or to a spot beneath the right shoulder-blade. Whereas cancer of the head of the pancreas is only a question of months, in cholelithiasis it may be one of years.

Pancreatic catarrh or chronic pancreatitis frequently accompanies gall-stones in the common duct and clears up after their removal, but it may persist after the cause has passed away. Whenever a tumour of the head of the pancreas is felt during a gall-stone operation, especially if before middle life, hope may always be felt that the disease may be simple and may clear up by the drainage of the ducts. A long history is in favour of the simple disease, as are the presence of adhesions, the history of painful attacks, and the presence of tenderness above the umbilicus. In chronic pancreatitis it is not uncommon to find enlarged glands in the free border of the lesser omentum, but they are discrete when the disease is simple and generally confluent in cancerous affections. The jaundice may be absolute, but, as a rule, it is not complete. Infective cholangitis and infection of the pancreatic ducts are commonly present, as shown by the temperature and by ague-like seizures. Although the loss of flesh is marked in chronic pancreatitis, it is less evident than in cancer of the head of the pancreas, and, until the disease has existed for a longer time than cancer gives its victim, there is no sign of anasarca or ascites or of enlarged abdo-

minal veins. The gall-bladder is seldom distended, though this is not an absolute rule, as in several cases we have had the opportunity of observing it much enlarged. Between gall-stones in the common duct and chronic pancreatitis (which frequently coexist) it is often difficult to determine, but this is of no moment from a practical point of view, as surgical treatment is, as a rule, demanded in both conditions. Anæmia is much more marked in cancer of the head of the pancreas than in chronic interstitial pancreatitis.

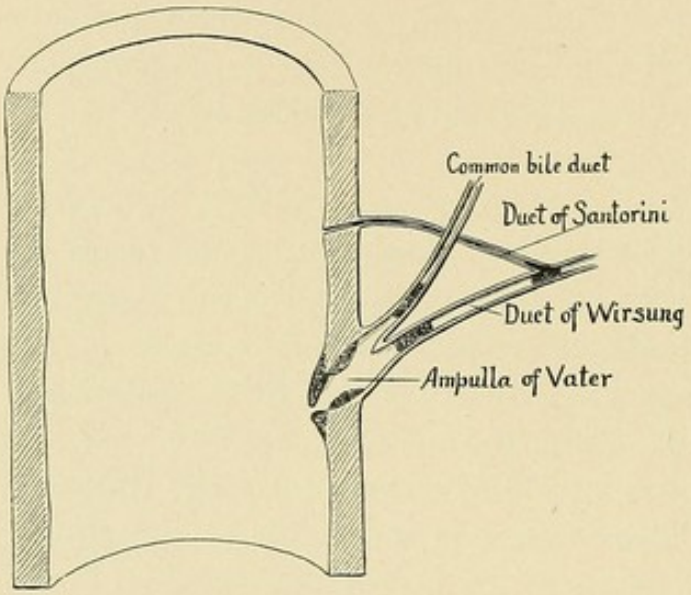


Fig. 172.—Diagram showing the sites of origin of malignant disease in the ducts and ampulla of Vater (modified from Rolleston).

Cancer of the common duct is rare and is usually associated with gall-stones; if the disease involves the papilla the symptoms are indistinguishable from those of cancer of the head of the pancreas; but if it be situated above the opening of the pancreatic duct, it will not interfere with the functions of the pancreas, and therefore the loss of flesh will not be so rapid. In two cases of cancer of the common duct in which we have made an analysis of the fæces they were found to be soft, white, and friable, like chalk or white Castile soap. No trace of stercobilin could be found in either instance. A quantitative estimation of the fats showed 90 per cent. of total fat, of which 32 per cent. was neutral fat and 58 per cent. combined fatty acid, in the one case, and total fat 83 per cent.,

consisting of 30 per cent. of neutral fat and 53 per cent. of combined fatty acid, in the other. Suppurative cholangitis is occasionally present, but this is not a constant event. The accompanying diagram shows the positions that growths may occupy in the neighbourhood of the papilla (Fig. 172).

Cancer of the liver is distinguished by the jaundice being absent or much less intense, and by the enlargement of the liver, with irregular nodules on its surface and edges.

In simple catarrhal jaundice the symptoms are almost negative, except for the jaundice and loss of appetite; and the way in which it yields to treatment shows the slighter nature of the ailment.

In cancer of the pylorus the predominance of gastric symptoms, the dilatation of the stomach, with absence of free hydrochloric acid and the presence of blood in the vomit, usually enable a diagnosis to be made, but it should not be forgotten that cancer of the pylorus and of the head of the pancreas frequently coexist. In all these cases the urinary test affords most valuable help in diagnosis.

Treatment.—Medical treatment must be purely symptomatic: morphine if needed for the relief of pain; calcium chloride for the prevention of hæmorrhage; pankreon tablets or liquor pancreaticus for the digestion of food; and other remedies for symptoms as they arise. Surgical treatment is not very hopeful and has usually been undertaken under the idea that the cause of the jaundice might be a removable one, or that drainage of the bile-ducts might afford relief to the jaundice, but if the disease has involved the head of the pancreas it is hopeless however treated.

Treatment may be radical or palliative. Ruggi, of Bologna, removed through the loin a cancer of the pancreas weighing 23 ounces. It was probably growing from

the tail of the gland. Complete recovery followed and the patient was well for three months, after which secondary disease developed and the patient died at the end of six months. Professor Ruggi himself has kindly furnished these details. Cades' was the second successful case, in 1895, a tumour of the tail of the pancreas of the size of a child's head being removed. Terrier, in 1892, removed a tumour weighing five pounds, but lost his patient. Of sixteen operations for removal of solid tumours of the pancreas, eight recovered, which, considering the difficulty of the operation and the depth of the organ to be operated on, is better than one would have expected. Successful pancreatectomies, it will be seen, are exceptional and are feasible only where the growth is not involving the head of the gland; they, however, clearly demonstrate that a tumour of the body or of the tail of the pancreas may be removed with equal chance of recovery, and should the disease be primary, and no secondary growths or glandular involvement have occurred, great prolongation of life is quite possible.

The palliative operations, cholecystotomy and cholecystenterostomy for the relief of jaundice in cancer of the head of the pancreas, have been performed by one of us in twenty-eight cases, all the patients being extremely ill at the time of operation. Many of these cases occurred when there was difficulty in making a diagnosis between cancer of the head of the pancreas and gall-stones in the common duct, or between cancer and interstitial pancreatitis, difficulties which have now been overcome to a large extent. Of the fifteen cases in which the gall-bladder was drained, eight recovered from the operation, the longest survival being eight months, but the average survival being about four months; of the six cholecystenterostomies, two recovered and the duration of life was only a few weeks. Even a simple exploratory operation in these cases is attended with danger, for out of six cases,

four only recovered from operation. Dr. Murphy, of Chicago, was kind enough to furnish a report of his collected statistics of cholecystenterostomy up to 1897. Of sixty-seven non-malignant cases there had only been three deaths, but of his twelve malignant cases ten died, giving a mortality of 83.3 per cent. Thus it will be seen that any palliative operation for the relief of cancer of the head of the pancreas associated with jaundice is useless, as, even if recovery occurs, life is not prolonged to any great extent.

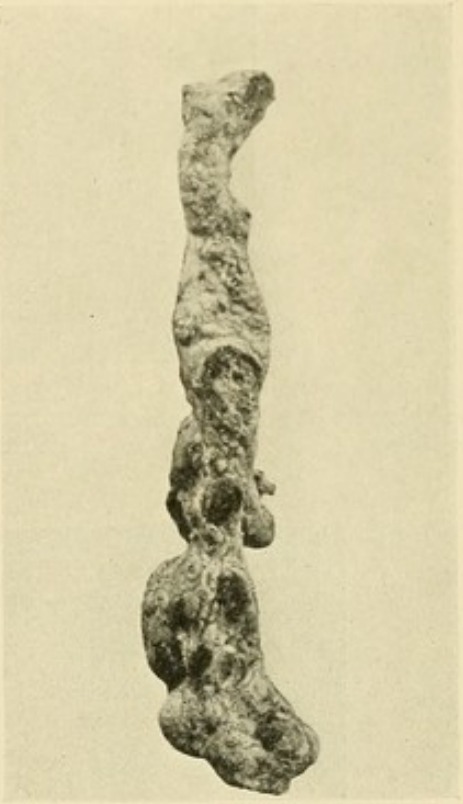


Fig. 173.—Melanotic sarcoma in the pancreas (Royal Coll. of Surg. Museum, 2836).

Sarcoma.—Primary sarcoma of the pancreas is undoubtedly rare, though secondary disease, especially of the melanotic type, seems to be less uncommon. There are examples of sarcoma in several of the museums, photographs of some of which are shown in the illustrations. The first is of melanotic sarcoma from the Hunterian Museum (Fig. 173). It was taken from a girl, aged twenty years, and was secondary to a melanotic growth in the eye, which was removed three years before her death. The next specimen is a very large spindle-celled sarcoma from University College Hospital Museum, No. 3200 (Fig. 174). The growth has completely destroyed the gland and has left no trace of gland tissue. The next specimen (Fig. 175), No. 2836 A, in the Royal College of Surgeons Museum, was removed from the tail

of the pancreas, but the child succumbed shortly after the operation.

Operation for sarcoma of the pancreas is uncommon,

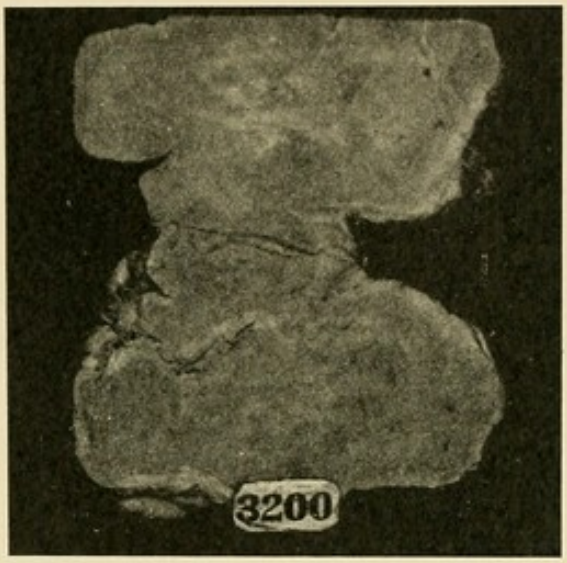


Fig. 174.—Spindle-celled sarcoma of the pancreas (Univ. Coll. Museum, 3200).

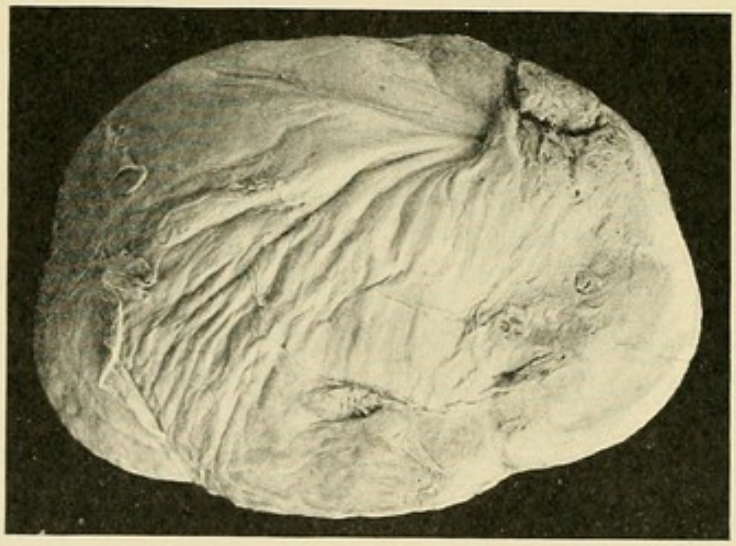


Fig. 175.—Sarcoma of the tail of the pancreas (Roy. Coll. Surg. Museum, 2836 A).

though the few cases operated on prove that if the tumour be in the tail of the pancreas the case is amenable to sur-

gical treatment. The abdomen was explored by one of us in a case of the kind, but the disease was found to be too extensive for removal. Krönlein, in 1894, removed a tumour of the size of the fist, but the patient died seven days later. A tumour which was successfully removed by Briggs proved to be sarcomatous degeneration of an echinococcus cyst.

Adenoma.—Adenoma of the pancreas is extremely rare. Instances have been recorded by Thierfelder, Biondi, Cesaris-Demel, Neve, and Nicholls. Several other cases described as adenomata were probably examples of malignant growths, and cannot therefore be included in the list. It is possible that some of the cases described as cystadenomata originated in simple adenoma, but, as this is uncertain, they are best for the present considered under the heading of cysts.

Diagnosis and Treatment.—Adenomata of the pancreas present no characteristic symptoms by which they can be distinguished during life, but should such a tumour be met with in the pancreas during the course of an exploratory operation an attempt should be made to extirpate or enucleate it.

Tuberculous Disease of the Pancreas.—Tuberculosis of the pancreas is usually considered to be rare, and as a pirmary lesion it undoubtedly is, but Kudrewetzki found that in a series of one hundred and twenty-eight cases of tuberculosis the pancreas was affected fifteen times, five times as part of an acute miliary tuberculosis, seven times as part of a chronic tuberculosis, and twice from tuberculosis in its neighbourhood. Children furnished the greater number, for he found 44.44 per cent. of pancreatic tuberculosis in tuberculous children, but only 9 per cent. in adults. He emphasises the fact that tuberculosis of the pancreas occurs only as a secondary condition in connection with tuberculosis of other organs. In Hale White's series of one hundred and forty-two post-mortems in which

the pancreas appeared to be diseased or injured there were four examples of tubercle. Three of the patients suffered from general tuberculosis and one from tuberculous peritonitis. He states that tubercle of the pancreas was found in considerably less than 1 per cent. of all cases of tuberculosis, and he therefore considers that it is a rare disease. Lohéac would explain the relative infrequency of tuberculous disease by virtue of the peculiar pancreatic secretion, which he thinks to be protective against this form of infection.

Tuberculosis of the pancreas may occur as numerous small, granular, infiltrating tubercles or as large caseous masses. The latter probably originate in most cases from lymphatic gland buried in the substance of the gland.

Treatment.—A few cases of successful removal of tuberculous masses from the pancreas have been recorded. Thus Sendler opened the abdomen of a thin woman, who had a movable tumour above the umbilicus, and found behind the stomach a hard mass the size of a walnut, which he extirpated. This proved to be a tuberculous lymph-nodule of the pancreas. The patient recovered. Kudrewetzki reports a case in which a caseous tuberculous mass burst into the stomach of a man of forty-two. The patient was operated on and a number of caseating glands found in the lesser omentum, but he became so collapsed on manipulating a tumour occupying the site of the head of the pancreas that nothing further was done. The wound healed and he was discharged.

Symptoms and Diagnosis.—At present it is impossible to diagnose tuberculosis of the pancreas during life, and since it is practically always secondary to disease elsewhere, its recognition is of no practical importance unless there are pressure symptoms.

Syphilis.—Syphilis, like tubercle, may occur in the pancreas in two forms, interstitial and gummatous, which may, however, coexist. Of the two, the former is

the more common. Both may result from either acquired or congenital disease.

In acquired syphilis disease of the pancreas is regarded as uncommon, but this may be due to there being no characteristic symptoms during life, in most cases, pointing to the pancreas. There is no reason why the pancreas should not be involved with other organs in visceral syphilis, which, being recognised and suitably treated, recover, for a gumma of the pancreas is just as likely to yield to treatment as gumma of the liver. Post-mortem records with regard to syphilitic affections of the pancreas are but meagre. Peterson in eighty-eight cases that had suffered from tertiary syphilis found only one in which the pancreas was affected.

Occasionally syphilitic disease of the pancreas may give rise to secondary symptoms; thus, H. Betham Robinson has given the details of a case in which there was obstructive jaundice due to a gummatous infiltration involving the head of the gland, in which cholecystocolostomy was successfully performed.

In congenital syphilis the pancreas is less commonly affected than the spleen or liver, but syphilitic deposits have been noticed as early as the fifth month. As a rule, the disease occurs as an interstitial inflammation starting from the vessels, but occasionally it occurs in the form of large or small gummatous masses. The interstitial overgrowth spares the islands of Langerhans, so that diabetes does not occur.

Treatment.—The surgical treatment of syphilis of the pancreas is limited to such cases as that of Betham Robinson above referred to, and reliance must be placed upon general medical means for dealing with this disease.

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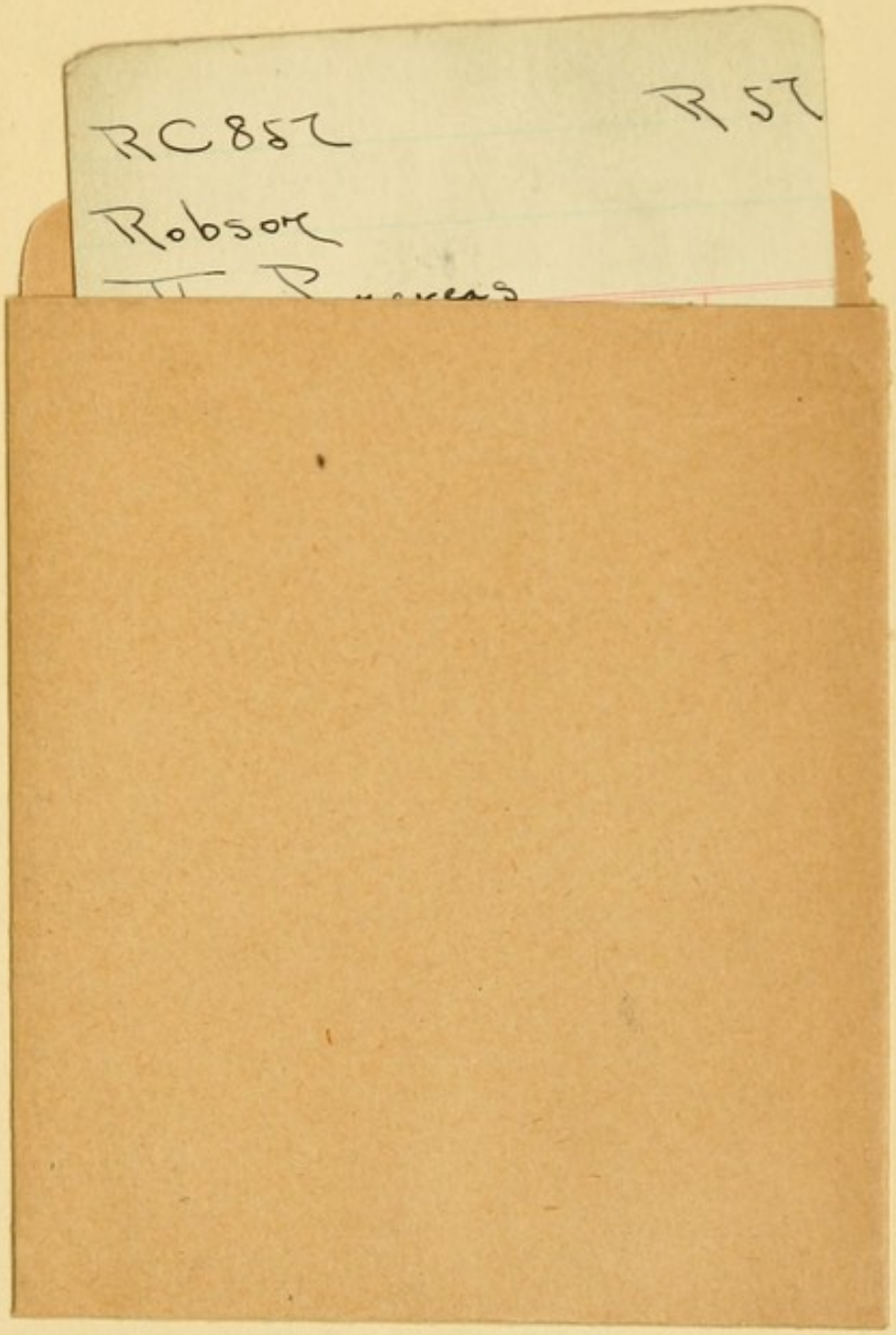
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