Remarks

ON

THE VALUE AND SIGNIFICANCE OF CERTAIN SIGNS AND SYMPTOMS OF PANCREATIC DISEASE.

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THE pancreas, like many other glands, has an internal and an external secretion. The internal secretion is the product of the islands of Langerhans, and controls the assimilation of sugars. The islands of Langerhans have no connexion with the secreting cells or with the ducts of the pancreas, and any pathological change in them produces, therefore, no alteration in the external secretion. The external secretion, poured into the second part of the duodenum at the diverticulum of Vater, is the most active and the most important of all the digestive juices. Diseases of the pancreas may affect the islands of Langerhans only, thereby interfering with the internal secretion, or with the parenchyma of the gland, thereby interfering with the external secretion, or, rarely, and in advanced stages only, the whole gland may be involved and both secretions may be lessened or abolished.

1. *Glycosuria and Diabetes.*

The association of diabetes with diseases of the pancreas was first pointed out by Cawley in 1788 in the *London Medical Journal*. Bright and other observers have confirmed the existence of the association by many recorded cases. The experimental work of von Mering and Minkowski, and later of Minkowski alone, showed that removal of the pancreas caused diabetes. The pancreas controls the carbohydrate metabolism, and loss of the organ is followed by diabetes. It was suggested by Laguesse, Schäfer, and others that the islands of Langerhans were mainly concerned in the exercise of this important function. Observations by Ssobolew, and finally and chiefly the original work of Eugene Opie, have proved beyond doubt that the internal secretion of the pancreas, which regulates the process of carbohydrate metabolism, is derived from the islands of Langerhans, and from them alone. Any lesion destroying the islands (a hyaline degeneration is the most common) results in diabetes.

The great complexity of the process of carbohydrate metabolism is shown, however, by the fact that other lesions affecting, for example, the nervous system, or certain toxic materials, may all result in glycosuria. But so far as the pancreas is concerned, it is solely by reason of the damage done to the islands of Langerhans that glycosuria follows upon any disease of this gland. Von Mering and Minkowski have further shown that if a portion of the pancreas only be removed, glycosuria does not develop. Minkowski, investigating the process of assimilation of sugars in a dog so operated upon, found that though glycosuria was not present when ordinary diet was given, yet it could be produced by increasing the sugar in the diet. The pancreas which remained, though adequate for the performance of the ordinary work, was unequal to the greater strain then put upon it. The condition so resulting is generally termed alimentary glycosuria. It has been further investigated by Wille.

In order to produce glycosuria in ordinary healthy individuals a dose of 150 to 250 gr. of glucose is needed. Wille administered 100 gr.—a quantity below the minimum mentioned—in $\frac{1}{2}$ litre of tea or coffee to 800 individuals. The urine was collected from each one at intervals of two hours, and the subsequent history of each individual was carefully noted; 77 of the patients died; of these, 15 had shown alimentary glycosuria; at the *post-mortem* examination a lesion of the pancreas was found in all, though in some the lesion was slight and only ascertainable on microscopic examination. In 4 cases of cancer of the pancreas, a positive result was given in 3. Though no diagnostic aid has been rendered as yet by this method, it is possible that, carefully regulated, it may prove of value. It will be necessary to discover in any case the minimum dose of glucose necessary to cause glycosuria, and also the quantity and percentage of sugar obtained from the urine. It is not unlikely that alimentary glycosuria may be shown to be present as an earlier manifestation or as a warning of pancreatic diabetes. If discovered in small quantity after the administration of the dose named, it will be suggestive of early changes in the

islands of Langerhans. It is probable that the measure of the glycosuria produced will be also the measure of the involvement of the islands of Langerhans.

The relationship existing between diseases of the pancreas and the condition known as "bronzed diabetes" is receiving careful investigation at the present time. There seems to be no doubt that in all cases which have been closely examined chronic interstitial pancreatitis has been present. In the condition described by von Recklinghausen as "haemochromatosis" there is a deposit of pigment in many of the organs of the body; this pigment was believed to be derived from the haemoglobin. In addition there is usually an enlarged and cirrhotic liver. The pancreas may also be affected, and when that is so the inflammation is of the chronic interstitial type, which finally involves the islands of Langerhans. Diabetes, therefore, is the result. Haemochromatosis has therefore as its natural termination diabetes of the "bronzed" type.

2. *Steatorrhoea.*

The presence of visible fat in the faeces was first recognized by Kuntzmann in 1820 as bearing a relationship to disease of the pancreas.

His patient was a man who died from chronic induration of the pancreas. There was complete obliteration of the common and pancreatic ducts, and dropsy was present. Large stools containing fat had been constantly seen. Bright, in his record of cases of disease of the pancreas, all accompanied by jaundice, found excess of fat in the faeces in three. The presence of an excessive quantity of visible faecal fat was noted by many observers subsequently. The fat was recognized at first in a liquid form, but later as a solid constituent of the faeces; the oil floating on the surface of urine passed at the same time being, of course, at once a matter for comment. In many of the early cases jaundice also was present, as well as the pancreatic disease, and some doubt was felt as to the influence of the lack of bile in the intestine in the causation of the fatty stools. Friedrich Müller, for example, attributed the steatorrhoea entirely to the absence of bile.

Claude Bernard, in his experimental work, destroyed the pancreas of a dog by injecting oil into the main duct. He found that fat was subsequently present in the faeces and often in such quantity that it formed a sort of coating to them. Abelman asserts that after total extirpation of the pancreas in dogs, all the unemulsified fat taken with the food reappears in the faeces. Other observers, however, have found that, even when no pancreatic juice enters the intestine, some of the unemulsified fat may be absorbed. Fitz of Boston, the pioneer in all the recent clinical work on the pancreas, in an address before the Congress of American Physicians and Surgeons in May, 1903, presented the following table (see p. 1741), which shows the relationship between visible faecal fat, jaundice, diabetes, and pancreatic disease.

This table, as Dr. Fitz remarks, does not support the view that jaundice is an important factor in the origin of the fatty stools connected with disease of the pancreas. It suggests that in about three-fifths of the cases of steatorrhoea attributable to pancreatic disease there is neither diabetes nor jaundice, that in two-fifths there is either diabetes or jaundice in about equal proportion, and in but few instances is there a combination of diabetes and jaundice.

Oser, in his work on the pancreas, describes the whole as being clay-coloured or white, and as being covered with or surrounded by an oily yellow fluid. Fles relates the remarkable case of a diabetic patient who had atrophy of the pancreas, and who ultimately died of phthisis. He daily passed with his stools a large quantity of fat, and a considerable quantity of unaltered, undigested muscle fibre. A fresh calf's pancreas (sweetbread) was well beaten in a mortar, with 6 oz. of water, and strained; the so obtained milky fluid was taken by the patient in separate doses, one after each meal, so that in this way an entire pancreas was consumed in the twenty-four hours; and although the previous diet, which largely consisted of bacon and fat meat, was continued, still, at the end of two days, all the fat, and in great part the undigested muscular fibre, had disappeared from the faeces. Each time the pancreatic infusion was left off the fat and muscular fibres again appeared. The favourable effects of the daily use of the calf's pancreas on the general health were exceedingly marked; the rapid emaciation seemed to be stayed, and the body to reassume its rounded proportions. The quantity of urine and the amount of sugar voided still remained entirely unaltered.

Lesion.	Stools.	Diabetes or Glycosuria.	Jaundice.	Authority.
Fibro-adenoma	Fatty	Present	Present	Biondi, Oser, Diseases of the Pancreas, Nothnagel's Encyclopaedia.
Cancer	"	Absent	"	Bowditch, Boston Med. and Surg. Journ., 1872, lxxvii, 65.
"	Like butter	"	Absent	Bright, Med. Chir. Trans., 1883, xviii, 1.
"Cyst"	Free fat	Present	Present	Bull, New York Med. Journ., 1887, 376
Calculi	Fatty	"	Temporary	Capparelli, Oser, op. cit.
Calculus passed	Fatty diarrhoea	Absent	Absent	Chopard, Oser, op. cit.
Cancer	Like butter	Present	"	Cipriani, Therap. Monats., 1898, xii, 617.
Atrophy, cong. syphilis	Like asbestos	Absent	"	Clark, Lancet, 1857, ii, 152
Calculus	Oily at times, like butter	"	"	Denne, Oser, op. cit.
"Cyst" atrophy, fibrous tissue in head of pancreas	Masses of fat crystals, once consistency of sweet oil	Present	"	Elliotson, Med. Chir. Trans., 1883, xviii, 77.
Indurated pancreas, obliterated duct	Fatty	"	"	Goodman, Trans. Path. Soc. Phil., 1878, viii, 41.
Cancer	Fatty before onset of diabetes	Absent	Present	Kuntzmann, Friedreich, op. cit.
Calculus, atrophy, growth of fibrous and fat tissue	"	Present	"	Labadie-Lagrave, Oser, op. cit.
Cancer	Fatty	"	"	Lancereaux, Bull. Acad. de Méd., 1888, xix, 183.
"	Grey, with white portions: fat with microscope	Absent	"	Luithlen, Oser, op. cit.
"	Fatty	"	Absent, bronzed	Mager, Wien. med. Pr., 1899, xl, 15.
Scirrhus of head, obliteration of duct	Very fatty, tenacious, slimy	Present	Present	Maragliano, Oser, op. cit.
Cancer	Fatty diarrhoea	"	Absent	Marsden, Amer. Journ. Med. Sci., 1854, xxviii, 212.
Enlarged pancreas, marked fatty degeneration	Fatty	Absent	Present	Martsen, Oser, op. cit.
Calculus, fibrous pancreas. Duct did not communicate with common duct or duodenum	Grey, greasy at times, solid, fat on cooling	"	"	Molander and Blix, Oser, op. cit.
Cancer	Fatty	Present	"	Motta, Union Méd., 1881, xxxi, 289.
Fatty degeneration	Oily	"	"	Phillips, Lancet, 1900, ii, 104.
Cancer	Fatty	Absent	Present	Pott, Oser, op. cit.
Cancer, closed duct	Silver grey, 25 per cent. fat	Present	Absent	Silver, Tr. Path. Soc., London, 1873, xxiv, 121.
Rarefied pancreas, obstructed pancreatic duct	Silver white consistency of salve	Absent	Present	Roques, Bull. Soc. Anat., 1857, ii, 245.
Pancreas appeared like fat. Calculus in duct	Free oil or fat	"	"	Ziehl, Deut. med. Woch., 1833, ix, 538.
		"	"	Müller, loc. cit.
		"	"	Walker, Med. Chir. Trans., 1889, lxxii, 257.

The presence of fat in the stools is, however, by no means pathognomonic of disease of the pancreas. As much as 5 per cent. or 10 per cent. of the fat taken into the stomach may normally pass away unabsorbed. In jaundice, even of the catarrhal variety, this amount is doubled at least. In certain diseases of the intestine, as Nothnagel and others have shown, and especially in diseases of the mesenteric glands, the amount of fat undergoes a large increase. Many observers, chief among them being Müller, have endeavoured to discover a special character in the fatty excrement characteristic of diseases of the pancreas. This observer endeavoured to show that a reduction in the amount of fat which had undergone cleavage, when the quantity of total faecal fat remained normal, was specially significant. The chemical analyses of the faeces made in cases of proved disease of the pancreas are, however, so few that no assured position can be taken in the question.

The stools, when the pancreatic secretion is absent from the intestine, are often quite characteristic. They are very bulky, pultaceous in consistence, and of a whitish or white-grey colour. This colour is still present, even when it can be subsequently shown that all the bile has passed into the intestine during life. It has been suggested that the stool is white because of the large amount of fat it contains—a view which is upheld by many. It is, however, also possible that the absence of the normal colour is due to the fact that the bile pigments are capable of absorption from the intestinal canal unless acted upon and made non-absorbable by the pancreatic juice.

The bulky fatty stools associated with chronic interstitial pancreatitis are often remarked upon by the patient. In two recent cases of this kind, in both of which the pancreatitis had been due to a stone which I had removed from the common duct, the stools were found to alter very rapidly after the administration of fresh pancreas by the mouth, together with regular quantities of pancreatic extract. The stools became natural in quantity, and the fat was reduced almost to the normal. The colour of the stools, however, did not show any marked change, a sufficient indication that their peculiar tinge was not due to the excess of fat alone.

The following conclusions may be stated:

1. Fat is normally present in the stools, about 5 to 10 per cent. of that taken in as food being discharged as unaltered.
2. If an excess of fat be taken in health, a proportionate excess of fat is found in the faeces.

3. In simple catarrhal jaundice, and in certain diseases of the intestine, the amount of fat in the faeces is approximately doubled.

4. Steatorrhoea as an isolated sign affords no evidence of pancreatic disease.

5. Steatorrhoea when associated with azotorrhoea in the absence of jaundice points strongly to disease of the pancreas.

6. Steatorrhoea, with azotorrhoea, diabetes, and epigastric tumour, is evidence of undoubted pancreatic disease.

3. Azotorrhoea.

The presence of undigested nitrogenous food, such as muscle fibre in the stools, was first recognized by Fles, in the case to which reference has already been made, as being a symptom of value in diseases of the pancreas. In this case chronic interstitial pancreatitis was found at the *post-mortem* examination; during life a large quantity of unaltered and undigested muscle fibre had been passed in the stools. Since the digestion of proteids in the intestine depends so largely upon the pancreatic juice, the absence of this juice in large or small amounts should be capable of recognition in the altered faeces. In certain cases of diabetes, which were possibly due to lesions of the pancreas, Hirschfeld found as much as 32 per cent. of the ingested nitrogenous material in the stools. Weintraud, in a case which was proved by autopsy to be one of chronic pancreatitis, found that as much as 45.2 per cent. of ingested proteids were discharged unaltered. Abelmann found that, after complete extirpation of the pancreas in dogs, 44 per cent. of the albuminous foods were absorbed; if a portion of the pancreas were allowed to remain, 54 per cent. of the foods were absorbed. Some part of the deficient absorption was ascribed by him to the presence of undigested fat in the intestinal contents.

Sandmeyer, after partial extirpation of the pancreas, found that as much as 70 per cent. of ingested albuminous foods might undergo absorption.

Azotorrhoea is an extremely inconspicuous symptom. In 8 cases observed by v. Ackeren, Fles, Harley, Lichtheim, Oser, Riegner, Teleky, and Müller, in which azotorrhoea was present with disease of the pancreas, in 6 sugar was present, in 5 there was steatorrhoea, and in 2 there was jaundice.

It is necessary, in examining a patient, to eliminate certain sources of error. If much meat be taken in the diet, or if there be a persisting diarrhoea, there will always be found, whether pancreatic disease be present or not, an excess of undigested muscle fibre in the faeces. As Fitz

very tersely and truthfully asserts, "any significant increase of undigested muscle fibres in the stools would be expected only when there was extreme diminution of pancreatic juice in the bowel, gastric digestion was relatively normal, the diet contained no excess of meat, and there was no diarrhoea."

In certain cases fat has been given in excessive quantity in the food to determine the activity of the pancreatic juice. Similarly it would be desirable to recognize in the first place the normal digestive power of an individual for proteids, and then to administer meat in excess in order to see the results thereby recognizable in the faeces. Meat, however, undergoes certain changes in the stomach, and, if possible, it would be desirable to introduce a proteid into the duodenum without having undergone any digestion in the stomach. Sahli suggested, that "glutoid" capsules containing iodoform or salol might be administered by the mouth with food. The coating of the capsules is so hardened by treatment with formalin, that it remains unaffected by the action of the gastric juice for several hours. As soon, however, as the capsule is passed onwards into the intestine, it is rapidly digested by the pancreatic juice, and its contents are liberated. Nencki has shown that salol is split up by the pancreatic juice into salicylic acid and phenol, and that the former is rapidly eliminated in the urine. If iodoform be used, the iodine reaction can be elicited from the saliva as soon as intestinal digestion is begun. In order that the test with the glutoid capsules should be accurate, there must be a normal activity of the gastric juice, a normal or nearly normal gastric motility, and a normal intestinal absorption. Failing any, but especially the two latter, the test loses much of its value. Sahli has related a series of cases in which the test showed absence of the reaction, or its delay for periods over twenty-four hours, and in which malignant disease of the pancreas was found. This test has since then been generally known as the "signe de Sahli." There has been so little purposeful investigation of this method that its value, though probably not small, has never yet been even approximately determined.

4. Fat Necrosis.

This condition was first described by Balser in 1882. In five cases opaque white areas, which microscopically proved to be composed of necrotic fat cells, were found in the fat around, and in the immediate neighbourhood of, the pancreas. In two cases the fat at some distance from the gland was affected also. Since these observations of Balser abundant confirmation of their accuracy has been made. The cause of the fat necrosis was discovered by Fitz. It was he who first suggested that a lesion of the pancreas was the determining and causative factor, and he drew attention to a series of cases in which the two conditions—pancreatic disease and fat necrosis—occurred together. The complete dependence of the fat necrosis upon disease of the pancreas is now universally admitted. The appearances caused by necrosis of the fat are quite typical.

Smaller or larger opaque, white unraised areas are seen studded irregularly in the fat; their colour contrasts in the most striking manner with the bright yellow colour of the fat. Near the pancreas the spots are larger, even a quarter or a third of an inch in diameter, and several of them may be confluent, so that a white streak results. The white areas are generally marked off abruptly from the surrounding tissues, but at times a bright red haemorrhagic zone may surround them. As a rule, the further the patches of necrosis are from the pancreas the smaller and the fewer are they. It is rare to find the fat outside the abdominal cavity affected, though the subcutaneous fat of the abdominal wall, and the pericardial fat, may be affected also. The nature of the fat necrosis was first shown by Langerhans. It consists in the splitting of the fat into fatty acid and glycerin; the fatty acids, deposited at first as acicular crystals in the cell, combine with the calcium salts to form a soap, while the glycerin is absorbed.

The immediate cause of the fat necrosis, whether localized or disseminated, has been shown to be the pancreatic secretion. The juice escaping from the gland diffuses more or less widely, and is in part, perhaps, taken up by the lymphatics. A fat-splitting ferment, probably that of the pancreatic juice, has been found by Flexner in foci distant from the gland, and Opie has possibly discovered its presence in the urine of a patient suffering from acute pancreatitis. Fat necrosis may, therefore, be said to consist in the action upon normal fat of the fat-splitting ferment of the pancreatic juice, which has

escaped from the duct as the result of some serious lesion of the pancreas. It is most commonly found in association with acute pancreatitis, of the haemorrhagic or gangrenous forms, but may also be found in association with chronic interstitial (interlobular) pancreatitis. The significance of fat necrosis is therefore considerable. If in any operation for some acute, but indeterminate, condition within the abdomen, a sharply-defined white, opaque, or ivory-like patch be seen in the omentum, or in any part of the intra-abdominal fat, the operation from being exploratory, becomes at once purposeful, and the pancreas is sought forthwith.

In one remarkable case related by Hansemann, bright red spots seen upon the skin were found to be due to underlying foci of necrosis in the fat of the abdominal wall.

The view that fat necrosis is wholly dependent upon lesions of the pancreas has been verified beyond dispute by the experimental work of Flexner and Opie.

5. Jaundice.

Jaundice is not uncommonly associated with diseases of the pancreas. Its existence is due to the anatomical relationship between the head of the pancreas and the common bile duct, and to the mode of termination of this duct and of the canal of Wirsung in the ampulla of Vater. In chronic pancreatitis or in malignant disease of the head of the pancreas, the enlargement of the gland causes pressure upon the duct from the outside, and, the calibre of the duct being narrowed, the free escape of bile is prevented and jaundice results. In calculus of the pancreas jaundice may be caused by the obstruction of the stone into the ampulla of Vater. Inflammation of the canal of Wirsung, of the mucous membrane of the ampulla, and of the common duct ensue, and the cholangitis is attended by jaundice. In acute haemorrhagic pancreatitis a slight tinge of jaundice has been occasionally observed. In many of these cases, as Opie has shown, the pancreatitis depends upon the retrojection of bile into the canal of Wirsung, as a result of the impaction of a biliary calculus in the papilla of Vater. A cholangitis exists in these cases also.

In cancer of the head of the pancreas the jaundice appears insidiously, deepens gradually, never varies in depth of tinge from day to day, becoming paler and deeper alternately, but progressively and without intermission becomes more and more pronounced. In many cases the gall bladder can be felt to be greatly distended. So constant is the rule that persisting jaundice associated with distension of the gall bladder depends upon cancer of the head of the pancreas, that it is now formulated as "Courvoisier's law," in deference to the distinguished clinician who first called attention to it.

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REPORT XC.

THE LYMPH-FLOW FROM THE PANCREAS.

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INTRODUCTION.

THE discovery of secretin by Bayliss and Starling has made it possible to obtain pancreatic juice at will; and in 1902 I showed that the injection of secretin caused, concomitantly with the secretion of pancreatic juice, an increased flow of lymph from the thoracic duct. This increase still occurred, though in smaller degree, after ligation of the portal lymphatics, and the lymph was therefore derived from either the pancreas or the intestines, presumably the former.

Recently, Falloise has carefully investigated the action of secretin on the lymph-flow. He found that secretin increased the lymph-flow from the thoracic duct, but that after ligation of the portal lymphatics the increase no longer occurred; ileum extract also caused an increased flow from the thoracic duct, notwithstanding that no pancreatic juice was secreted. On the other hand, secretin solutions, when freed from albumoses and depressor substance, caused a flow of pan-