The Schorstein Lecture

ON

THE DIAGNOSIS OF DISEASE OF THE PANCREAS.

DELIVERED AT THE LONDON HOSPITAL MEDICAL COLLEGE
ON FEBRUARY 20TH, 1920.

BY

SIR ARCHIBALD E. GARROD, K.C.M.G., M.D.,
LL.D., F.R.S.PHYSICIAN TO AND DIRECTOR OF MEDICAL CLINIC AT ST. BARTHOLOMEW'S HOSPITAL; REGIUS PROFESSOR OF MEDICINE DESIGNATE,
UNIVERSITY OF OXFORD.

He who is commemorated in a memorial lecture is often but a dim figure of the past, for whom and for whose work the lecturer can feel only a platonic admiration; but it is a very different matter when one does homage to a man whom he has known and liked, a member of his own university, and a dweller in the next street. Such was Gustave Schorstein, whose too early death left, for all who knew and valued him, a gap not easily filled, a sense of loss of a talented and attractive personality. I esteem it a great privilege to be permitted to pay this tribute to his memory.

This lecture should have been delivered five years ago, but the war and its duties intervened. Now that we are at peace once more, and are trying to make up the time lost during "the years that the locust hath eaten," the invitation has been renewed, and for that honour it is my pleasant duty to return my thanks.

In point of diagnostic display the liver and the pancreas, both glands of many vital functions, may be compared to a shop window and an office door. Derangement of the work of the shop may be obvious to the passer-by in the street, whereas what goes on behind the ground glass of the office door is hidden from public view, and is only manifested in the indirect effects of disorder of the activities within. If only the pancreas produced such a coloured secretion as the bile, how much easier would be the diagnosis of many of its lesions!

As it is the position of the pancreas, sufficiently remote to shield it from examination but not from injury, and the fact that its secretion is poured into so inaccessible a region of the alimentary canal, enabled it for a long time to puzzle the physiologist and to baffle the physician.

In the middle of the last century Sir Thomas Watson,¹ in one of those delightful lectures of his which, in lucidity and literary style, rank with those of Trousseau, spoke as follows: "It may seem a slight to the pancreas to pass it over without noticing the diseases to which it is subject. But really these diseases appear to be but few; and they do not signify their existence by any plain or intelligible signs." Somewhat later Bristowe,² in his well known textbook of medicine, expressed his belief that in the great majority of cases pancreatic disease will doubtless remain undetected during life. But some other writers of that period struck a more hopeful note, and among them Wardell,³ who, in 1871, wrote: "No symptoms are pathognomonic of pancreatic disease; an assemblage of symptoms indicates the probability of its lesion." These words still hold true to-day, and they embody the thesis of this lecture.

It is true that we have learnt to recognize in fat necrosis a sign pathognomonic of certain lesions of the gland; but since this is only made manifest by opening the abdomen it lends us no help at the bedside. One other sign has been claimed as distinctive—namely, true steatorrhoea, which was recognized by Kunzmann⁴ as early as 1824, and independently by Richard Bright⁵ in 1832, as indicative of pancreatic disease.

Even nowadays pancreatic lesions often escape diagnosis, and Paul Carnot⁶ puts his finger upon the cause of many such failures in the following passage: "Le plus difficile est, souvent alors, de songer au pancréas, étant donné la rareté apparente des affections de cette glande." The more constantly we bear the pancreas in mind as a possible seat of origin of obscure abdominal troubles, the less likely shall we be to overlook its lesions. The diagnostic indications, at our disposal fall into three main groups. In the first are the clinical signs and symptoms, such as tumour, pain, tenderness, vomiting, cyanosis, and

the like, and the signs of pressure upon neighbouring structures. Secondly, we may detect signs of failure of external secretion, defective digestion of proteins, fats, and carbohydrates. Thirdly, indications of failure of internal secretion, of which glycosuria is at the same time the most important and the best known.

TABLE I.—Pancreatic Signs and Tests.

Physical Signs and Symptoms.	Defects of External Secretion.	Defects of Internal Secretion.
Aspect Tumour Pain Tenderness Cyanosis Vomiting Constipation Diarrhoea Jaundice	Steatorrhoea Fatty stools Creatorrhoea Impaired casein digestion Duodenal sound Einhorn's method Oil breakfast	Glycosuria Lowered sugar tolerance Cambridge's tests
Sympathetic signs Ocular Loewi's test	Sahli's capsules Schmidt's test Kashiwado's nuclear test Sajodin test Diastase test, in urine and faeces.	

Lastly, there are certain syndromes which clinical and pathological experience has taught us to associate with lesions of the pancreas. Thus the diagnosis of carcinoma of the head of the gland is often correctly made upon purely clinical evidence, and in cases of bronzed diabetes, with enlarged cirrhotic liver and peculiar pigmentation of the skin, the pancreas is always implicated.

Many ingenious tests of pancreatic efficiency have been devised, and each test has its adherents, and each its critics who question its utility. But surely we are wont to ask too much from such tests. We cannot look to any test for a penny-in-the-slot diagnosis, especially of such widely diverse lesions as those to which the pancreas is liable. At best we cannot hope to gain more than an item of circumstantial evidence which, taken in conjunction with other items, may contribute to a diagnosis of probability, or even of certainty. Taken alone each test may fail or may actually mislead. In some instances a negative, and in others a positive, response carries little weight, and one needs to get to know a test well before he can estimate the significance of its answers.

It is not my intention, nor would it be possible in a single lecture, to describe the many pancreatic tests. In my wards we have employed most of them in turn, and in cases of special difficulty have resorted to many. For some years before the war we were interested in this subject, and it is to the help of a group of active fellow workers that I owe most of such knowledge of it as I possess. I would specially mention my indebtedness to my former house-physician, Dr. Sladden, who has embodied his conclusions in two valuable papers,⁷ and to Dr. Mackenzie Wallis, whose M.D. thesis on this subject I have been permitted to read, and who has forgiven me beforehand if I should encroach upon his ground in advance. To Dr. Hurley, to my assistant Dr. G. Graham, and to Dr. Geoffrey Evans also, I am grateful for much valuable help.

Where there is so great a choice of tests, workers tend naturally to concentrate upon some few which have seemed to them especially useful and easy of application. Each one develops his own routine, and different workers make different choices. The tests upon which one man relies do not necessarily serve another best.

The physical signs and symptoms of disease of the pancreas are best seen in cases of acute pancreatitis, although the large cysts which sometimes spring from the gland produce far more conspicuous swellings, and it is with carcinomata that the pressure signs are most clearly manifested. Nevertheless, the diagnosis of acute pancreatitis is by no means easy in many cases, and the most common false diagnosis is one of acute intestinal obstruction.

A grossly enlarged pancreas forms a tumour in the upper part of the abdomen, lying between the xiphoid cartilage and the umbilicus. It does not move with respiration, and has often but an ill-defined outline. The natural dullness on percussion is obscured by the overlapping of the stomach and intestine. In favourable

cases, in thin subjects, and especially under an anaesthetic, it is even possible to feel a pancreas which is only slightly enlarged, and some have claimed to have felt the normal pancreas. By percussion over the back Dr. Ewart maintains that the size of the gland may be mapped out with considerable accuracy.

The pain of pancreatic disease may be continuous or paroxysmal; it is felt in the abdomen, and is liable to be confused with other acute abdominal pains. My own experience and that of my colleague Mr. Waring, which is considerably greater, leads us to attach much more importance to pain across the back than do most of those who have written upon the subject, and in cases of carcinoma of the pancreas also such pain is often a prominent symptom.

In acute pancreatitis vomiting is usually severe, obstinate constipation tends to strengthen the suspicion of intestinal obstruction, and a feature which has some diagnostic value is a slight degree of cyanosis. The abdomen is usually distended, but, as a rule, there is less rigidity of the muscles than in other acute inflammatory lesions within it.

Of pressure symptoms referable to the diseased pancreas jaundice is by far the most conspicuous, and, in view of the anatomical relations of the gland to the common bile duct, this is in no way surprising. In cases of carcinoma of the head of the gland the jaundice is of extreme degree, and the complete absence of urobilin from the stools shows that the bile duct is completely occluded. Oser⁷ suggests, and Sir Mayo Robson⁸ also holds, that the so-called catarrhal jaundice may often have its origin in a swelling of the pancreas. We have as yet little knowledge of the slighter inflammatory affections of the gland, but there is one variety the clinical features of which are fairly well known—namely, that which occurs as a metastasis of mumps. Some years ago Dr. Cammidge told me that of eight cases of mumps with abdominal symptoms he had found his test positive in four, and in one of these it was no longer obtained after an interval of a month. Glycosuria was present in one case. Barbieri⁹ has recorded a case of temporary glycosuria with this affection, and Finizio¹⁰ one with transitory steatorrhoea, with as much as 60 per cent. of neutral fat in the stools. I have been able to find only a single record of an autopsy in such a case, and in that case alone was jaundice one of the symptoms. Lemoine and Lapasset,¹¹ who described it, found the pancreas swollen, oedematous, congested, and of a reddish-grey tint.

The absence of jaundice in almost all cases of the pancreatitis of mumps seems to me to afford a strong argument against the connexion of catarrhal jaundice with a catarrhal pancreatitis; and it is certainly no common feature of cases of grave pancreatitis, haemorrhagic or other.

On the other hand, there is, as Mayo Robson has shown, a close connexion between gall-stone troubles and interstitial pancreatitis, and from the anatomical relations of the biliary and pancreatic ducts an infection of the one is likely to spread to the other. So jaundice with pancreas lesions may have other origin than in compression of the bile duct. A tumour of the pancreas may cause considerable obstruction of the duodenum also. Watson mentions this in his lecture already referred to, and actual obstruction may occur in those rare instances in which the head of the gland encircles the duodenum completely. Again, there may be signs of pressure upon the portal vein and vena cava.

In a short paper, published in 1912, Cohn and Peiser¹² called attention to the presence in some cases of pancreatitis of the ocular symptoms which we associate with undue activity of the thyroid gland. Of a series of five cases, three of haemorrhagic, one of suppurative, and one of chronic interstitial pancreatitis, they found some exophthalmos in four, von Graefe's sign in four, Moebius and Stellwag's signs in all five, and also tremor and dermatoglyphy in all. However, they wisely decline to draw any sweeping conclusions from so small a number of cases.

Shortly after reading their paper I was able to confirm their observations in a case of which I shall speak later. The association clearly calls for further study, and has very interesting bearings upon the wider subject of interaction of the thyroid gland and pancreas, of which I hope to treat at greater length on some future occasion.

The experience of many of us who have been engaged

on military duties in recent years has taught us to look for signs of hyperthyroidism in conditions which we did not formerly connect with the thyroid gland, and to recognize that the characteristic case of Graves's disease is merely the culminating point of a series of intermediate grades which bridge the gap between it and normality. Moreover, we have witnessed a dissociation of the thyroid symptoms, one patient showing the ocular signs alone, and another tachycardia with tremor. Indeed, it would seem that there are several thyroidal hormones, and that excess of one does not necessarily carry with it excess of another.

Of such conceptions we have long had glimmerings, as witness the use of the term "larval Graves's disease."

As a rule, when thyroidal and pancreatic symptoms are seen in association, the thyroid appears to be the organ primarily at fault, and the observations of Cohn and Peiser, for which the converse holds good, are of all the greater interest on that account.

But if in pancreatitis the eye symptoms referred to are due to excessive thyroid secretion, it is really the sympathetic nervous system which is stimulating the gland to over-activity, and it is not wonderful that the sympathetic should be disturbed when the pancreas is the seat of disease, seeing how near a neighbour it is of the great abdominal ganglia and plexuses. Indeed, many of the symptoms of acute pancreatitis, the severe and often paroxysmal pains, the vomiting and collapse, are, by many, attributed to this proximity. There is evidence, too, of a restraining effect of the pancreas upon the excitability of the sympathetic, an influence which is withdrawn when the pancreas becomes the seat of disease.

It was to test the existence of such a soft-pedal influence that O. Loewi¹³ applied his adrenalin mydriasis test to depancreatized cats and dogs. The extension of his observations to human subjects led to the introduction of one of the most interesting, although not one of the most conclusive, of the tests of pancreatic efficiency.

Two or three drops of a 1 in 1,000 solution of adrenalin, freshly prepared, are dropped into the conjunctival sac, and the process is repeated after an interval of five minutes. In the great majority of instances no dilatation of the pupil occurs, but in a few cases there is conspicuous dilatation in the course of half an hour or an hour. The dilated pupil is usually excentric in position, and often conspicuously oval in form. When Loewi first tried the test upon normal people, and upon a series of patients in the Vienna clinics, mydriasis was seen only in 1 of 3 cases of exophthalmic goitre and in 10 out of 18 diabetics. Apparently there were no cases of gross pancreatic disease in the series. Loewi regarded the positive results in some cases of diabetes as indicative of a pancreatic origin, but attributed the mydriasis in the case of exophthalmic goitre to the irritability of the sympathetic in that disease.

Of recent years we have employed Loewi's test widely in my wards, and in my opinion it is of undoubted value in the diagnosis of pancreatic lesions, provided always that its ways have been studied and that its limitations are fully recognized.

The dilatation of the pupil is a decidedly uncommon phenomenon. Unlike Loewi, I have seen it in very few cases of diabetes in which there was no other evidence of lesions of the pancreas, and I have obtained it only once in exophthalmic goitre. We have failed repeatedly to obtain dilatation when the test was repeated, within a day or two, upon an eye which had previously dilated, whereas the mydriasis was again brought about after a longer interval.

The pupils need to be carefully examined before the adrenalin is applied, not only as to their equality, but also to make sure that the iris of the eye tested is mobile. We have been deceived in one case by trying to dilate a pupil fixed by synechiae, and the dilatation is inhibited for a time by the administration of morphine.

The test may fail, at a later stage, in a case in which dilatation had occurred at an earlier period. It may fail in a case in which there is definite disease of the pancreas, and may succeed in another in which there is no gross lesion of the gland. All this sounds very discouraging, but the experience gained in a large number of cases has taught me to regard adrenal mydriasis as strongly suggestive of a pancreatic lesion, and to look upon it as a valuable link in a chain of evidence pointing to such a lesion.

On the other hand, I would *never* venture such a diagnosis upon this reaction alone, nor should I conclude from the absence of any dilatation that the pancreas was intact. Of few of the tests of pancreatic efficiency can more be said.

One of the drawbacks of Loewi's test is that it is, if anything, too delicate, and is wont to give a positive response to a lesion which merely worries the pancreas without involving it to any noteworthy extent. Against this may be set the advantage that the dilatation of the pupil is apt to be most marked at a stage when the excretory functions of the gland are not as yet seriously impaired.

The indications of abeyance of the external secretion of the pancreas, which now claim our attention, are the most valuable aids to diagnosis that we possess, and upon such evidence alone a secure diagnosis may in some cases be based. We may look for failure of the digestion of proteins, fats, and carbohydrates alike, for, unlike any other digestive gland, the pancreas takes an important part in the digestion of all three classes of foodstuffs. But, in my opinion, the signs of failure of digestion of fats are the most significant of all.

If there be any single sign which, standing alone, may be regarded as pathognomonic of disease of the pancreas it is true steatorrhoea. By this is meant the passage with the faeces of liquid fat which solidifies on cooling.

Salomon¹⁴ speaks of it as a sign observed only with pancreatic disease, and for my own part I should not hesitate to share his view but for a case which Dr. Hurlley and I investigated some years ago.¹⁵ The patient, a boy then 7 years old, had passed oil with his motions from birth. A younger brother who died of measles at 11 months had exhibited the same anomaly, whereas the three other children had not. The parents are first cousins. The boy was otherwise in good health, well grown, and with no trace of infantilism. Last month I saw him again after an interval of six years, and found that the same still holds good. Although many tests were applied no other sign of lesion of the pancreas could be found, and, in spite of the defect of fat utilization, the digestion of proteins was not impaired, and the stools contained no undigested meat fibres. Apparently this boy is the subject of an inborn error of metabolism, probably due to the absence of a normal enzyme, presumably a pancreatic enzyme. It is difficult to believe that there is any real disease of his pancreas.

There are grounds for the belief that both the external and internal secretions of the pancreas take part in the utilization of fats, the lipase being concerned with the splitting of fats, the internal secretion with their absorption. The gross failure of fat-splitting, which Friedrich Müller¹⁶ described as so characteristic of lesions of the pancreas, may be lacking in cases in which there is conspicuous excess of faecal fat in association with such lesions, and experience teaches us that the total fat content of the stools, made up of fats, fatty acids, and soaps, affords a safer guide. Better still is the information supplied by the far more laborious estimation of the proportion of the fat taken in the food which is lost in the faeces. When, in addition, there is a conspicuous failure to *split* fats the evidence of a lesion of the pancreas is so much the more cogent. In the stools of a healthy man some 75 per cent. of the fat is in the split form, whereas some patients with pancreatic disease pass as little as 20 per cent. in the forms of fatty acids and soaps. The great diagnostic significance of true steatorrhoea arises from the fact that it indicates not only an excess of fats in the stools, but also an undue proportion of neutral fat.

In cases with no gross steatorrhoea the microscope may show abundant fat globules and many acicular crystals of fatty acids. Moreover, the large bulk of the fatty stools may arrest attention, and in some cases they are justly described as elephantine.

The jaundice which is so often associated with obstruction of the pancreatic duct obscures to some extent the indications afforded by the estimation of the faecal fats, for the mere absence of bile from the intestine causes a great impairment of fat absorption; but even when the pancreatic duct alone is blocked widely divergent results are obtained in different cases. Moreover, in the majority of cases of disease of the pancreas there is no blockage of the duct, and the impairment of secretion results from

damage to the glandular tissue and is less in degree. A patient with grave disease of the pancreas may pass stools with normal fat-content, and this is true even of some cases in which the duct is obstructed, probably because the duct of Santorini remains patent and provides an emergency outlet.

Even when jaundice is present a proportion of fats in the dried faeces exceeding 40 or 50 per cent. is strongly suggestive of a pancreas lesion, and in some cases there is a percentage of 80 or more.

L. Zoja¹⁷ lays stress upon an unduly low proportion of soaps as indicative of pancreatic disease, presumably from a deficient supply of alkali in the intestine, but our own experience, and that of others, leads us to attach little importance to this sign.

Oskar Gross,¹⁸ who made a very complete study of the fat excretion of two patients with indubitable disease of the pancreas, found that in one case the percentage of the food fat lost in the faeces remained constant, in spite of wide variations in the amounts in the diet, and Hurlley and I found the same to be true for our case of congenital steatorrhoea; but in Gross's second case, and in that investigated by Spriggs and Leigh,¹⁹ the loss of fat became much greater when the fat in the diet was increased. The last named observers suggest that the constant percentage loss may only hold good for cases in which the patient's nutrition remains good. It is a remarkable phenomenon, and one not easily explained, but upon which future work may throw light.

It will be seen, from what has gone before, that a patient whose pancreas is diseased may pass excess of neutral fats in his motions, or a great excess of fats, fatty acids and soaps, without any undue proportion of neutral fat. Lastly, a lesion of the pancreas can by no means be excluded on the ground that the stools contain no excess of fatty substances.

Winternitz has introduced a test of the efficiency of the pancreas in dealing with fats. Half a gram of iodo-behenic acid, or the drug sajodin, which is its calcium salt, is given by the mouth, and iodide is looked for in the urine. The sajodin is only broken up when it comes under the influence of the pancreatic juice, and by it *only* in presence of bile. On this account the test is not applicable when the bile duct is completely obstructed. When there is no jaundice, failure to find iodine in the urine suggests that the lipolytic action of the pancreas is in abeyance.

When in addition to impaired splitting or utilization of fats there is obvious failure of protein digestion, the evidence of a pancreatic lesion is wellnigh conclusive. There are many ways in which such failure may be detected, but the simplest of all is at the same time the most convincing. A patient with severe pancreatic disease will, as a rule, pass in his faeces large numbers of muscle fibres, derived from the meat which he eats, undigested and with their striae clearly visible under the microscope. He may also pass particles of undigested tissue, and Albu²⁰ recommends calf's thymus as an article of diet the structure of which is easily recognized in the stools. For this phenomenon Ehrmann suggested the name "creatorrhoea," by which it is generally called; and although the term invites criticism it is not easy to invent a better.

Creatorrhoea, although it may accompany profuse diarrhoea from any cause, is hardly inferior to fatty stools in diagnostic value, and it has the advantage that it is not affected by blocking of the bile duct. In a case with jaundice in which the indications afforded by the faecal fat are not unequivocal, the discovery of undigested striped muscle fibres in the stools may help materially to clinch an otherwise doubtful diagnosis.

Cases are met with in which the syndrome steatorrhoea-creatorrhoea persists for years, in a patient who otherwise enjoys moderately good health, who leads an active life and exhibits no other gross sign of disease. Some such patients have been found to have the duct blocked with calculi, and the structure of the gland destroyed, and yet may never have exhibited glycosuria. In these cases the more elaborate tests will, as a rule, afford additional evidence of disease of the pancreas.

Excessive excretion of nitrogen in the stools, and a consequent inordinate loss of nitrogen as determined by metabolism investigations, affords additional evidence of impairment of protein utilization, but other ferments

besides trypsin take part in this work, and azotorrhoea, so called, is far less distinctive than the escape of striped muscle fibres and nuclei. Moreover, the fatty stools of a patient with pancreatic disease offer a far from ideal material for Kjeldahl estimations.

The majority of the pancreatic tests are concerned with the failure of tryptic digestion. They fall into three main groups of procedures: Some of them aim at obtaining a sample of duodenal contents for examination; others rely upon the dispatch of messengers along the alimentary canal, and the examination of the stools or other secretæ for evidence as to what has happened to them in their transit; and yet others upon estimation of the tryptic action of the faeces.

The oil-breakfast test relies upon the fact that, under its influence, some of the contents of the duodenum are regurgitated into the stomach, and may be found in the test meal when it is siphoned off. The technique of the test is comparatively simple, and its results are, as a rule, instructive, but the swallowing of a large dose of olive oil, 2 oz., with a test meal, upon an empty stomach, and its subsequent withdrawal, is a proceeding which has little attraction for the British patient. It has been clearly shown that it is possible to obtain a sample of the secretion in the duodenum, either by means of a suitably constructed duodenal sound, or, better still, by Einhorn's ingenious device of a small metal capsule cased in gelatin and attached to a string or to an india-rubber tube. The capsule is swallowed and is passed on into the duodenum by gastric peristalsis. It is well to check its progress by x-ray examination. By this means as much as 5 to 10 c.cm. of duodenal juice may be obtained in favourable cases, and its tryptic activity tested. I have no experience of these methods, and therefore am not in a position to judge of the value of the indications which they afford, nor of the degree of discomfort to the patient which their application may entail. It is obvious that there are possibilities of fallacy, and that, whereas the finding of trypsin in the juice affords positive evidence that pancreatic secretion is entering the duodenum, the failure to find it in the fluid obtained is far less conclusive as evidence of inefficiency of the gland.

Of methods which test the tryptic power of the faeces that of Oskar Gross is most often employed. It is based upon the digestion of casein by an alkaline extract of the faecal material. Failure to digest casein offers strong evidence of pancreatic inefficiency, but, seeing that other ferments in faeces can act like trypsin, a positive outcome of the test, unless very pronounced, has less value.

What may be called the messenger tests are of several kinds. Thus Sahli administered capsules of gelatin hardened by formalin, and enclosing a drug easily detected in the urine or saliva. Provided that the capsule is well made, it is only amenable to tryptic digestion, and escape of the drug is taken to indicate tryptic activity; but a negative finding is far from conclusive. The capsule may resist tryptic digestion, especially if its journey along the alimentary canal be unduly rapid. It is only necessary to mention Schmidt's beef-cube test, and Kashiwado's in which stained nuclei from the calf's thymus are swallowed, mixed with lycopodium granules, the latter to serve as indicators of the part of the faeces to be searched. Sladden, who tried this test on several of my patients, obtained no very encouraging results, and compares the search in the bulky faeces of a patient with pancreatic disease to the proverbial hunt for a needle in a haystack.

It seems to me preferable to rely rather upon such gross phenomena as creatorrhoea and steatorrhoea as indicators of inefficiency of the pancreas, than upon the somewhat uncertain responses of these messenger tests.

To pass on to the consideration of carbohydrate digestion. It was shown by Wohlgemuth, whose observations have been abundantly confirmed, that a diminished output of diastase in the stools, and an increase of that enzyme in the blood and urine, are common phenomena in cases of lesion of the pancreas, and it would seem that we are here dealing with a sort of colourless jaundice, due to an obstructed flow of the pancreatic juice into the intestine, or else to a direct escape of diastase into the blood, comparable to that of lipase which brings about fat necrosis. But there are indications that the explanation of neither of these events may be so simple. However this may be, the estimation of diastase in the urine affords one of the best and most useful tests of the integrity of the pancreas,

and at the same time one of those most easily and rapidly carried out. This last is an important matter when we are dealing with acute conditions, in which delay of surgical interference may greatly lessen the prospect of its success. The diastase and adrenalin mydriasis tests may be carried out within an hour, whilst the patient and the theatre are being prepared for an operation. But the diastase test shares the uncertainty which pertains to pancreas tests in general. Instead of the normal ten to twenty, or even thirty, units, to use the accepted measures of the test, a patient with pancreatic disease may excrete in his urine fifty, a hundred, or even two hundred units. On the other hand, another patient similarly affected may show a normal diastase excretion. Mackenzie Wallis emphasizes the fact that the diastase increase is a temporary incident, most conspicuous in the earlier stages of a case. Repeated examinations at intervals may reveal a quicker or slower decline of the diastase output until normal, or even subnormal, figures are reached. Thus it comes about that whereas a conspicuous excess of diastase in the urine is strongly suggestive of disease of the pancreas, a normal excretion, such as was found by Spriggs and Leigh in their case, in no way excludes even advanced disease of that gland.

Nor must it be forgotten that in many cases of renal disease the power of the kidney to excrete diastase is so seriously impaired that its estimation in the urine is utilized as a test of renal efficiency. This deprives the indications of most of their value, for our purpose, in cases with albuminuria. Again, like Loewi's reaction, the diastase test errs on the side of excessive delicacy. Both tests may give positive answers when, so to speak, the pancreas is merely worried by adjacent disease. Thus, when both these tests yield positive findings, strong evidence, stronger by far than either alone supplies, is afforded that the pancreas is at least concerned in the malady; but apart from other indications they are in no way conclusive. Of the two, I attach greater importance to the diastase findings. Undoubtedly the failure of both tests in no way excludes serious pancreatic mischief.

There remains to be considered the evidence of failure of internal secretion of the gland. Since the classical researches of von Mehring and Minkowski, glycosuria has occupied a foremost place among the signs of pancreatic lesions, but, from the clinical standpoint, it is far from fulfilling the promise held out by physiological experiments. Whereas it is highly probable that the pancreas is concerned in all cases of glycosuria, save, perhaps, those in which the proportion of sugar in the blood is below the normal, it may well be that in most cases of diabetes the hyperglycaemia and glycosuria result from a disturbance of the normal balance between the pancreas and other endocrine glands, with the result that its internal secretion is inhibited or overpowered. We know that an excess of thyroid secretion may cause glycosuria although the pancreas be intact, and the same holds true for pituitary secretion and adrenalin.

On the other hand, experiments show that a small residue of pancreatic tissue may avert glycosuria, and it is a matter of common knowledge that the gland may be gravely damaged, and even to all appearance destroyed, by disease, and yet the patient may excrete no sugar in his urine. Indeed, it may be said that, except in cases of chronic pancreatitis, glycosuria is an uncommon symptom of pancreatic disease. I am inclined to think that daily observations throughout the illness would reveal the presence of sugar in the urine at times in many more cases than appears at present. In an acute case I have met with it in one single specimen and never afterwards. In cases of carcinoma of the head of the pancreas glycosuria is less rare than might be expected, seeing how large a part of the gland usually escapes invasion, and how little time is afforded for the development of secondary changes. Miraillé²¹ found it in 13 out of 50, and Guillou²² in 20 out of 71 cases.

Speaking generally, the absence of glycosuria affords no argument against the presence of disease of the pancreas, but in not a few cases its presence supplies the crowning evidence in support of a diagnosis based upon other findings. Lastly, even those who attribute all diabetes to disease of this gland will hardly maintain that the presence of glucose in the urine is in itself sufficient evidence of

such disease. Even in chronic interstitial pancreatitis glycosuria is by no means always present, and Opie²⁸ attributes the difference in this respect to differences in the incidence of the lesion, which in some cases involves, and in others spares, the islands of Langerhans.

Short of actual glycosuria, the patient's tolerance for glucose may be so far lowered that quantities of that sugar far smaller than are required to induce glycosuria in a healthy subject, cause glucose to appear in the urine. Thus tests of sugar tolerance are among the diagnostic means at our disposal; but it must be remembered that almost any disturbance of the balance of the internal secretions leads to an alteration, either a raising or a lowering, of glucose tolerance.

Cambridge's reaction, which may be fitly referred to in this place, is a phenomenon of much interest, the further investigation of which may throw light upon important metabolic events. It is undoubtedly connected with pancreatic derangements, and when observed supplies a contribution to the building up of a diagnosis. But it shares the uncertainty of other pancreatic tests, and may fail us in cases of severe disease of the gland, especially when the disease has reached an advanced stage. So it is natural that many prefer to employ methods which are less time-absorbing, and less at the mercy of small errors of technique. This test has suffered from the fact that too much has been expected from it, perhaps that too much has been claimed for it; and because it has not proved so decisive as was hoped its utility has not received the credit which it deserves. Of Cambridge's iodine coefficient method, which is a development of his original test, I have had no experience.

In this survey of the methods at our disposal for the diagnosis of lesions of the pancreas I have presented to you the separate pieces of a jig-saw puzzle. Only when the several pieces have been fitted together can we form a distinct clinical picture of pancreatic disease. Nor must we forget that when we have determined the seat of a lesion we have attained to only half of a diagnosis. We need to diagnose the nature of the lesion also. As it happens this is, in the conditions under discussion, the less difficult problem of the two.

In the endeavour to diagnose the nature of the more common diseases of the pancreas, such as acute pancreatitis, carcinoma, cysts, and chronic interstitial pancreatitis, we rely mainly upon the evidence afforded by physical signs and symptoms. Here clinical experience, when fortified by the experience gained in the post-mortem room, is our best guide, although we may derive no little help from the grouping of the responses of the various tests. Even pancreatic calculi have been diagnosed and removed with success; but it is probable that there will long remain a residuum of cases in which we have reason to believe that the pancreas has been damaged by disease, but in which the nature of the lesion cannot be determined with any degree of accuracy.

In order to illustrate some of these aspects of my subject it will be necessary to place before you brief records of a few characteristic cases, and to indicate the steps by which a diagnosis was arrived at in each instance. The examples chosen were wholly unlike in their general features, and had little in common beyond the fact that in all but one of them the pancreas was or is undoubtedly implicated in disease. Each one illustrates some special diagnostic points.

Case 1.

A man, aged 50 years, a street salesman, was admitted to hospital complaining of abdominal pain. Seven weeks previously he had been thrown from a van, struck his head and abdomen, and was rendered unconscious for a short time. After the accident he suffered from severe pain in his back and vomited each morning. Three days later he returned to work, although he felt very unwell and the vomiting continued. A fortnight before his admission he noticed swelling of the upper part of the abdomen, and was obliged to loosen his belt. Five days later he was seized with a violent pain, of sudden onset, with sweating and collapse. The pain was relieved by hot fomentations. From that date the abdominal swelling increased, the vomiting persisted, his bowels were confined, and he suffered much from thirst. He was

brought to the hospital after a second attack of severe abdominal pain.

The man's appearance was suggestive of grave illness; his expression was anxious, his skin moist, and there was a slight degree of cyanosis. His temperature was only 99°, his pulse 110, and respirations 24 in the minute.

Situated in the upper part of the abdomen, midway between the xiphoid cartilage and the umbilicus, was an ill-defined elongated mass, overlapped in part by the gastric resonance. A band of resonance, 1½ inches wide, separated the mass from the hepatic dullness. The tumour did not move with respiration, and no fluctuation could be made out. The abdomen was somewhat distended, but the muscles were not rigid. There was no free fluid in the abdominal cavity. The patient complained of severe pain in the back, across the lumbar region. The mass was very tender, but the greatest tenderness was over the left flank.

It is worthy of note that there was exophthalmos of slight degree; von Graefe's sign was pronounced, and he wrinkled his forehead very little when he looked upwards. A well marked tache could be elicited, but there was no tremor of the hands.

The physical signs and symptoms pointed to a subacute pancreatitis following the injury to the abdomen, and when a specimen of urine was obtained and found to contain sugar, little doubt remained as to the correctness of the diagnosis. My colleague, Mr. Waring, saw the patient with me and concurred, and an operation was decided upon. Meanwhile Dr. Graham estimated the sugar in the blood at 0.21 per cent.; Loewi's reaction was positive but not of an extreme degree, and Dr. Mackenzie Wallis found 50 units of diastase in the urine. At the operation the diagnosis was confirmed. The pancreas was explored and drained.

The man lived six weeks after the operation. On the third day Moebius's sign was present, and von Graefe's persisted, but all the eye signs disappeared before the end. A second specimen of urine obtained before the operation contained no sugar, and none was found at any subsequent examination.

Case 2.

In March, 1919, a carman, aged 59, was admitted to my wards deeply jaundiced, and with a history of three months' illness. On examination his liver was found to be greatly enlarged and of smooth surface; the gall bladder was not palpable. Some enlarged glands were felt in the abdomen. Occult blood was found in the stools, but urobilin was wholly absent—signs which suggested that a malignant growth had occluded the bile duct. Although the clinical features were so unlike those of a classical case of carcinoma of the head of the pancreas, so well described by Bard and Pic,²⁴ in that the liver was so large, the gall bladder was not palpable, and the patient was neither emaciated nor unduly feeble, the possibility of such a growth was considered, as also that of a malignant growth originating in the bile ducts. It soon became evident that wherever the growth started the pancreas was implicated, and for the following reasons:

Adrenalin caused a conspicuous mydriasis on several occasions; the urinary diastase amounted to 125 units; the total fats of the faeces constituted no less than 70 per cent. of the dried material, and many undigested striped muscle fibres were seen in the faeces.

A week after his admission sugar appeared in the patient's urine for the first time, and the glycosuria persisted until his death. The average daily output of glucose was about 35 grams.

The fat content of the faeces, which was far greater than the jaundice could explain, increased as time went on, whereas the urinary diastase fell gradually from 125 to 60, 25, and 30 units, figures scarcely above the normal.

The patient died after he had been in hospital two and a half months. At the autopsy carcinoma of the head of the pancreas was found; there were no secondary growths in the greatly enlarged liver which had completely hidden the gall bladder which latter, although greatly distended with bile, had never been palpable during life.

Case 3.

The next case to which I shall refer could not be subjected to any systematic investigation. A man,

aged 53, was first seen by me in October, 1910, at the request of his medical attendant, Dr. Robbs. His complaint was that for six months past he had passed oil with his stools, which became solid fat on cooling. In twelve months he had lost a stone of weight. He suffered no pain of any kind. Nothing abnormal could be found on examination of his abdomen; his liver was just palpable; there was neither fullness nor tenderness in the region of the pancreas and there was no jaundice. His urine contained neither sugar nor albumin.

When I saw the patient again, in June, 1913, he had lost another stone, but had developed no fresh symptoms, and his urine was still free of sugar. He was still able to lead an active life. Loewi's test gave no mydriasis, and the urinary diastase did not exceed the normal.

Dr. Cammidge examined his urine and faeces, in January, 1914, and obtained a positive reaction with his test. The total fat in the dried faeces amounted to 51.2 per cent., and of this only 4 per cent. was in the form of soaps. There was obvious creatorrhoea with many undigested muscle fibres in the stools, and by means of Gross's test casein digestion by faecal material was found to be very incomplete.

Dr. Robbs tells me that now, in 1920, the patient's health is better than for some time past, and he has gained seven pounds of weight during the past six months.

Case 4.

The last case is that of a Belgian refugee, aged 32, who was admitted to my wards in January, 1915. For three years he had been liable to paroxysmal attacks of pain, referred to the region between the xiphoid cartilage and the umbilicus. During the attacks, which were obviously very severe, the patient assumed a position of opisthotonos, but he never vomited. It was suspected that he might have a pancreatic calculus, but the x rays showed no shadow in that region. Loewi's reaction was conspicuously positive, and the urinary diastase was at first 100 and afterwards 50 units. There was no excess of fat in the stools, no glycosuria, and only 0.12 per cent. of sugar in the blood. Thus the only indications of pancreatic disease were the position of the paroxysmal pain, the excess of diastase in the urine and the adrenal mydriasis. Our investigation of his symptoms was much hampered by the fact that he spoke only Flemish, and a very few words of English.

A month after his admission he passed a large tarry motion. A few days later Mr. Waring performed gastrojejunostomy. A few days after the operation the patient developed bronchopneumonia, with maniacal delirium, of which he died. At the autopsy a chronic ulcer was found in the second part of the duodenum, three-quarters of an inch in diameter and adherent to the pancreas and adjacent structures. The note describes the pancreas as normal to the naked eye.

If we review these four cases we notice how widely different were the clinical pictures which they presented. In the first case the diagnosis rested mainly upon the clinical signs and symptoms, but several tests of pancreatic efficiency supported the clinical diagnosis. In the second case, that of carcinoma, the evidence of a lesion of the pancreas rested largely upon disturbances of the external and internal secretion of the gland, but was quite conclusive. The only point in doubt was the primary seat of the growth. Except the intense jaundice the clinical signs did not afford much help.

In the third case the associated steatorrhoea and creatorrhoea leave no doubt that the patient is suffering from a severe pancreatic lesion, and Cammidge's test gives further support to this view. Presumably the duct is obstructed, and the pancreas is the seat of interstitial changes. The absence of pain does not exclude the presence of calculi. The failure of the adrenalin and diastase tests in no way invalidates the diagnosis. The case resembles one described by T. J. Walker²⁵ of a patient whose steatorrhoea persisted from the age of 62 until his death at the age of 90, and whose pancreas was found to be completely obsolete and replaced by fat, and the duct was studded with calculi. In cases in which a like syndrome is presented with glycosuria in addition the patient's health is much more seriously impaired, and the prognosis is far more unfavourable.

In the last case, that of the Belgian, we can hardly escape the conclusion that the disturbance of the pancreas by the adjacent ulcer was the cause of the increase of urinary diastase and of the adrenalin mydriasis.

In a case of bronzed diabetes which has been described at length elsewhere²⁶ we employed several pancreatic tests. Of these Loewi's test, Schmidt's beef-cube test, and the glycosuria pointed to implication of the pancreas, whereas Cammidge's test, the estimation of fat in the faeces, and the determination of the tryptic and diastatic activity of the stools gave no indication of damage to that gland. After death the pancreas was found to be fibrotic, and loaded with iron-containing pigment.

In the case of congenital steatorrhoea, on the other hand, there was no creatorrhoea, the faeces digested casein; Sahli's capsule test and that of Schmidt, a normal diastase content of the urine, and the absence of adrenalin mydriasis, all tended to acquit the pancreas. Cammidge's test alone, kindly carried out by its author, was found to give a "slightly positive result."

TABLE II.

Case.		Loewi's Test.	Fatty Stools.	Creatorrhoea.	Casein Digestion Test.	Sahli's Test.	Schmidt's Test.	Urinary Diastase.	Glycosuria.	Jaundice.	Cammidge's Test.
1	Subacute pancreatitis ...	+	—	—	—	—	—	+	+	0	—
2	Carcinoma of head of pancreas	+	+	+	—	—	—	+	+	+	—
3	Blocked duct, chronic pancreatitis	0	++	+	+	—	—	0	0	0	+
4	Duodenal ulcer adherent to head of pancreas	+	0	0	—	—	—	+	0	0	—
5	Bronzed diabetes, chronic pancreatitis	+	0	?	0	—	+	—	+	0	0
6	Congenital steatorrhoea	0	++	0	0	0	0	0	0	0	?

+ Signifies positive; ++ true steatorrhoea; 0, negative; — not tried.

It will be evident from all that has gone before that practically every sign, symptom, or test may fail us at times, and that in each individual case we need to balance the quantity and quality of the evidence for and against a lesion of the pancreas. In a word, we come back to Wardell's statement of 1871. It is still true that "no symptoms are pathognomonic of pancreatic disease; an assemblage of symptoms points to the probability of its lesion." But we have at our disposal a far greater assemblage of symptoms than Wardell had, and in not a few cases the degree of probability is not to be distinguished from certainty.

That is as much as can be expected when we are dealing with a problem the solution of which rests so largely upon circumstantial rather than direct evidence. If we cannot claim for the diagnosis of pancreatic disease the clear-cut, direct answers obtained in some other regions of clinical medicine and surgery, we may none the less regard with complacency what has so far been accomplished in this field by the application of physiological discovery at the bedside, by the co-operation of the laboratory and the ward.

REFERENCES.

- 1 Watson, *Lectures on the Principles and Practice of Physic*, fifth edition, ii, 689.
- 2 Bristowe, *Theory and Practice of Medicine*, fourth edition, 1882, 779.
- 3 Wardell, *Reynolds's System of Medicine*, 1871, iii, 411.
- 4 Kunzinann, *Journ. d. prakt. Heilkunde*, 1824, x, 124.
- 5 R. Bright, *Med.-Chir. Trans.*, 1833, xviii, 1.
- 6 P. Carnot, *Traité de Méd. et de Thérapie* (Brouardel et Gilbert), vol. xx, 124.
- 7 Oser, *Die Erkrankungen des Pankreas*, 1898, 111.
- 8 Mayo Robson, *BRITISH MEDICAL JOURNAL*, 1910, i, 975.
- 9 Barbieri, *Gazz. degli Osped.*, 109, xxx, 273.
- 10 Finizio, *La Pediatria*, 1909, 2 ser., vii, 674.
- 11 Lemoine et Lapasset, *Bull. et mém. Soc. Méd. des Hôpitaux*, 1905, xxii, 640.
- 12 Cohn and Peiser, *Deut. med. Woch.*, 1912.
- 13 O. Loewi, *Arch. f. exper. Path. und Pharmacol.*, 1908, liv, 83.
- 14 Salomon, *Die deutsche Klinik*, xii (Ergänzungsband 1), 533.
- 15 Garrod and Hurler, *Quart. Journ. of Med.*, 1913, vi, 242.
- 16 Friedrich Müller, *Zeitschr. f. klin. Med.*, 1887, xii, 45.
- 17 L. Zoja, *Il Morgagni*, 1898, xl, Pt. I, 617, and 1899, xii, Pt. I, 1.
- 18 Oskar Gross, *Deutsches Archiv f. klin. Med.*, 1912, cviii, 106.
- 19 Spriggs and Leigh, *Quart. Journ. of Med.*, 1915, ix, 11.
- 20 Albu, *Beiträge zur Diagnostik der inneren und chirurgischen Pankreaserkrankungen*, Halle, 1911.
- 21 Miraillet, *Gazz. des Hôpitaux*, 1913, lxvi, 889.
- 22 Guillou, quoted by Carnot.
- 23 Opie, *Disease of the Pancreas*, second edition, 1910, 213.
- 24 Bard et Pic, *Rev. de Méd.*, 1888, viii, 257; 1897, xvii, 920.
- 25 Walker, *Med.-Chir. Trans.*, 1899, lxxii, 257.
- 26 *Quart. Journ. of Med.*, 1914, vii, 129.
- 27 For references for special tests see Sladden's papers, *Quart. Journ. of Med.*, 1914, vii, 455, and St. Bartholomew's Hospital Reports, 1913, xlix, 19.