ISLET-CELL TUMOURS OF THE PANCREAS: WITH REPORT OF THREE CASES.

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The history and development of knowledge of tumours of the islets of Langerhans is intimately associated with the progressive understanding of the physiology of these minute structures and of their relationship to diabetes mellitus. The early experiments in this subject have been reviewed by many authors and are well known. Following the classical work of Banting and Best (1922) on the extraction of insulin, it was found in the course of treating diabetes with the new and as yet poorly standardized insulin that excessive dosage was followed by a definite train of symptoms sometimes culminating in coma and always associated with low blood sugar levels, (Banting *et al.*, 1923).

In 1923 Harris postulated that hypoglycaemic symptoms might well occur spontaneously due to hyperinsulinism in the non-diabetic subject and he set about looking for such cases. By June, 1924, he was able to collect three cases with fasting blood sugar levels below 70 mg. per 100 ml. in which improvement was obtained by feeding carbohydrates. It was not until 1927 that the first islet-cell tumour of the pancreas associated with hypoglycaemia was found. This, on operation, proved to be a metastasizing carcinoma, and publication of the findings by Wilder *et al.* (1927) greatly stimulated interest on the subject. In 1929, the first successful removal of an islet-cell adenoma in a case displaying hypoglycaemic symptoms was reported by Howland *et al.*, and since then the recorded cases of complete surgical cure exceed a hundred. This operative success has been associated with a remarkably low mortality rate. Knowledge of islet-cell tumours has naturally increased over this period and there is a number of excellent reviews and original contributions, *e.g.*, O'Leary and Womack (1934) ; Whipple and Franz (1935) ; Campbell *et al.* (1939) ; Conn (1940, 1947) ; Duff (1942) ; Whipple (1944) ; Franz (1944) ; Lopez-Kruger and Dockerty (1947) ; Conn and Hinerman (1948).

The striking effects of hypoglycaemia induced by a proportion of islet-cell tumours prompted Lopez-Kruger and Dockerty (1947) to subdivide them into functioning and non-functioning types according to the presence or absence of hypoglycaemic symptoms. Each group was further classified into adenomata, carcinomata, and tumours bordering on malignancy.

Adenomata. The incidence of islet-cell adenomata cannot be accurately assessed from the examination of hospital records and routine pathological reports. This is in part due to the relatively recent recognition of such tumours, but more particularly to the fact that in post-mortem examinations small pancreatic adenomata, especially the non-functioning variety, can very easily be overlooked. According to Lopez-Kruger and Dockerty (1947), Pease, in a careful examination of the pancreas at 500 consecutive necropsies, found 8 islet-cell tumours which apparently had not produced hypoglycaemic symptoms. Two were pea-sized and six were microscopic. This incidence of 1 in 62 necropsies makes interesting comparison with Pappenheimer's figures (quoted by Whipple & Franz, 1935) of 5 tumours (4 non-functioning) in 4,010 consecutive ordinarily conducted necropsies, an incidence of 1 in 800 necropsies.

Age Incidence. On the average, non-functioning adenomata occur rather later in life than the functioning type ; thus the great majority of the former type are found in people over 50 years old while the average age of cases of the latter is 41-45 years. As Duff (1942) suggests, this difference can probably be ascribed to the functioning tumours revealing its presence either by giving rise to symptoms which prompt its removal or cause death, whereas the non-functioning adenoma is an incidental necropsy finding, death having resulted from causes unrelated to the presence of the tumour, and therefore occurring usually later in life. He implies that the tumours were present for a long period before death, a view supported by the fibrosis with hyalinization and calcification found in many such tumours.

In the functioning tumour, the clinical history may give an indication of the age of the tumour ; thus the average duration of symptoms before operative removal or death is between 4 and 5 years ; such tumours may, however, prove fatal in a much shorter time, and Kerwin (1942) reports a case which died in hypoglycaemic coma 16 days after the onset of symptoms.

Size. The great majority of functioning adenomata are rounded tumours of 1-2 cm. in diameter : Duff (1942) stated that no tumour of less than 1 cm. in diameter had been known to give rise to hypoglycaemic symptoms, but more recently Lopez-Kruger and Dockerty (1947) report two functioning tumours of 2.5 mm. and 4 mm. in diameter respectively. The non-functioning adenomata tend to be rather small, usually with a diameter of less than 1 cm. The largest exception to this generalization is a tumour measuring 13 × 8 cm. (Cottalorda & Escarras, 1933).

Site. In most cases the tumours occur within the normal boundaries of the pancreas, but both functioning and non-functioning tumours have been found in ectopic sites, and it seems true that wherever ectopic

pancreatic tissue may be found so also may these adenomata. Approximately 70 per cent of the tumours occur in the body and tail of the pancreas (Lopez-Kruger & Dockerty, 1947). This is of importance to the surgeon who may be confronted with cases in which the tumour is not discernible at operation, because the chances are that partial pancreatectomy, leaving the head *in situ*, will effect removal of the tumour. The occurrence of multiple tumours, from two in number to a diffuse adenomatosis of the islets, has been reported (Franz, 1944; Lopez-Kruger & Dockerty, 1947). O'Leary and Womack (1934) and Whipple and Franz (1935) report cases in which removal of a tumour has been followed by persistence of symptoms and exploratory laparotomy has revealed a second tumour, the removal of which effected complete cure.

Carcinomata. Lopez-Kruger and Dockerty (1947) have collected from the literature 17 cases of islet-cell carcinomata with hyperinsulinism. They show that, as would be expected, the survival period after the appearance of the first symptoms is usually short, averaging about a year. Various authors have drawn attention to the obesity which sometimes occurs in a metastasizing malignant tumour. This apparent paradox is due to the large carbohydrate intake such patients have been forced to adopt in an attempt to alleviate the symptoms of hypoglycaemia. Apart from the direct evidence in metastases these tumours have shown unequivocal evidence of malignancy in cytological character and in local behaviour.

In the absence of hypoglycaemia, it is difficult to be certain that any pancreatic carcinoma is of islet-cell origin, which probably accounts for the rarity of reported non-functioning islet-cell carcinoma. Duff (1942) was able to find only 6 such cases.

Borderline Tumours. There are also islet-cell tumours which might be described as bordering on malignancy. These neoplasms exhibit cytological features which are doubtfully malignant and they also show local evidence of infiltration by their deficiency of encapsulation and the frequency with which local venules are invaded. Duff (1942) argues that these tumours are in fact benign while Lopez-Kruger and Dockerty (1947) feel that they are probably of a low-grade malignancy, but prefer to withhold definite opinion until the cases now being studied by them have been under surveillance for longer periods.

CASE REPORTS.

As illustrative examples of islet-cell tumours with and without hypoglycaemia, the following three cases are reported.

Case 1. The patient, a woman of 49, was admitted to hospital in a state of coma. Her principle symptom had been transient phases of unconsciousness during the previous four days. Each of these phases had been manifested initially by a cry, and the subsequent period of unconsciousness had persisted for 10-15 minutes. It was later learned that she had had a single attack of unconsciousness about a year previously.

Examination. The complexion was slightly pale, nutrition was good, and breathing was quiet. Respiration-rate was 20 per minute with appreciable periods of apnoea. Temperature was 101.6° and pulse-rate 116 per minute. The skin surfaces were normally moist and free from rash.

Examination of the central nervous system revealed negative responses to stimulation of the usual afferent pathways to consciousness. On passive elevation of the eyelids, the pupils were seen to be circular, equal and central; they dilated perceptibly on exposure to daylight but contracted, within a minute, subsequently, in response to the light of an electric torch. This contraction was followed by a definite phase of hippus. The tendon reflexes were normally active throughout the body while the abdominal reflexes were absent and the plantar responses extensor on both sides. There was no nuchal rigidity and Kernig's sign was negative. Urinary incontinence was present. Ophthalmoscopic examination revealed clear discs and normal calibration of the retinal vessels. Apart from tachycardia, the heart presented no abnormal signs. B.P. 140/110. Crepitations were present at the bases of both lungs. Abdominal examination was entirely negative.

Blood examination revealed a leucocytosis of 16,400 per cu.mm. On lumbar puncture, the fluid was clear and under normal pressure; the response to Queckenstedt's test was normal. Cells were 7 in 3 cu.mm. and Pandy's test showed a faint haze with 6 drops. The colloidal gold reaction was negative.

The first specimen of urine after admission was acid and contained protein (1 part Esbach). Sugar, ketones and chlorides were absent. The centrifuge deposit showed no casts, no crystals, and no organisms. Subsequent specimens of urine were protein-free. On admission, blood-urea was 200 mg. and blood-sugar 50 mg. per 100 ml.

Treatment and subsequent progress. Treatment consisted of intramuscular penicillin at 3 hourly intervals (in all 300,000 units daily for 5 days), and intravenous fluids, 20 pints of physiological saline and 12 pints of 5% glucose, during the 5 days after admission. The patient remained comatose although the depth of coma appeared to fluctuate: at times she seemed to be on the threshold of consciousness, when reflex blinking was elicited in response to the light of an electric torch; this was particularly noticeable on the day preceding death. The urinary output was about 500 ml. daily and the blood-urea fell to 110 mg. per 100 ml. Terminally, the temperature rose to 106°, breathing became Cheyne-Stokes in type and the patient died on the sixth day after admission to hospital.

Necropsy findings. Necropsy was performed 24 hours after death. The body was that of a middle-aged woman, well-nourished but not obese, and showing no external evidence of disease. The only abnormality in the thoracic viscera was an early bilateral acute broncho-pneumonia in both lower lobes. In the alimentary tract, abdominal and pelvic viscera, no gross abnormality was detected. The meninges were normal, and the blood-vessels around the base of the brain were healthy. The brain showed no surface abnormality, and on section no focal lesion was found. It was noted, however, that the grey matter was of a uniform violet-pink colour; the white matter also appeared congested.

Careful examination of the pancreas revealed a small nodule in the tail of the organ, and incision showed a discrete rounded solid tumour 8 mm. in diameter, completely enclosed in pancreatic tissue and situated near the lower border 6 cm. from the tip of the tail. The tumour appeared to be enclosed in a thin capsule; it was of the same yellow-grey colour as the surrounding pancreatic tissue and discernible mainly because the cut surface was solid and homogenous, contrasting in this respect with the fine lobulation of the pancreatic tissue.

Histology of the tumour. The tumour had the appearance of a benign islet-cell adenoma, being composed of groups of cells closely resembling those of the islets of Langerhans.

At the periphery, the stroma blended with a thin and irregular connective tissue capsule which extended as fibrous strands between the groups of acini of the surrounding pancreatic tissue (Fig. 1). In most parts of the tumour, and particularly at the periphery, the stroma appeared as a network of delicate connective tissue rich in capillaries and enclosing groups of tumour cells (Fig. 5). Towards the central part of the tumour the stroma was coarser and formed thick strands of relatively avascular fibrous tissue (Fig. 2). The groups of tumour cells were traversed by capillaries accompanied by a few reticulin fibrils (Fig. 3), the vascular arrangements being thus similar to those of the normal islet of Langerhans (Fig. 4).

The appearances and arrangement of the tumour cells are illustrated in Figs. 5, 6 & 7; they present (*a*) solid alveolar, (*b*) duct-like and (*c*) elongated ribbon-like

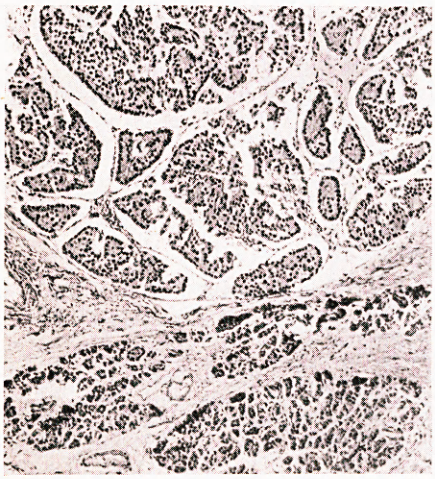

Fig. 1. Case 1. The darkly-staining exocrine pancreatic elements contrast with the paler tumour cells which are seen to be arranged in groups enclosed in a fine stromal network. The capsule of the tumour is thin and indefinite, fibrosis extending into the adjacent pancreatic tissue. Haematoxylin and eosin. × 75.

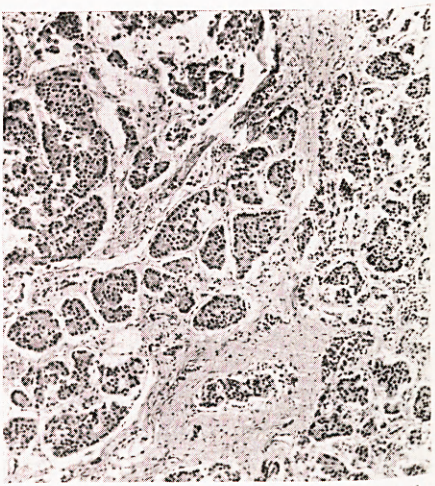

Fig. 2. Case 1. A field from the central part of the tumour where the stroma consists of coarse bands of relatively avascular fibrous tissue. Haematoxylin and eosin. × 75.

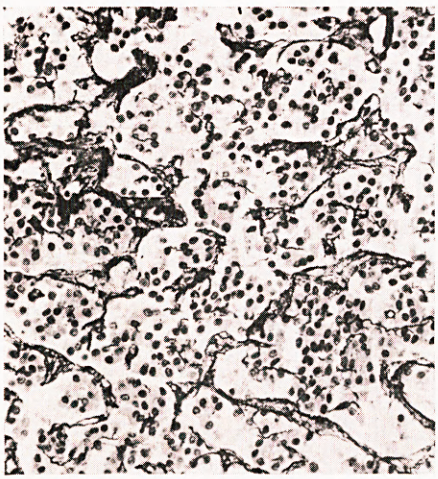

Fig. 3. Case 1. A silver impregnation preparation of part of the tumour, showing the clusters of tumour cells to be traversed by capillaries ensheathed in a few reticulin fibrils. × 240.

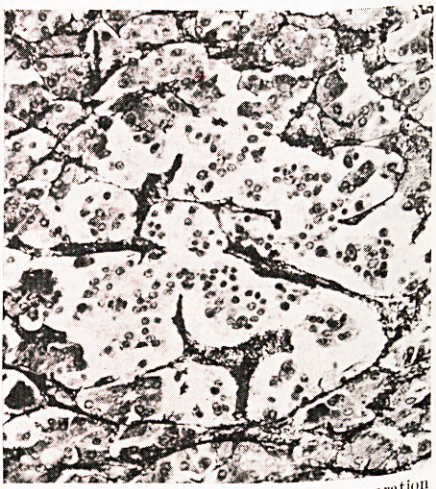

Fig. 4. Case 1. A silver impregnation preparation of a pancreatic islet, showing the reticulin accompanying the capillaries which traverse the islet. × 240.

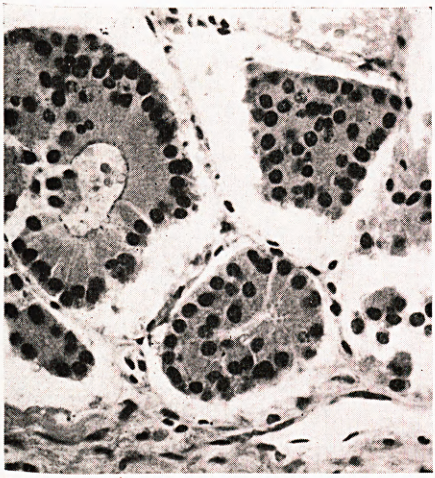

Fig. 5. Case 1. Three groups of tumour cells are seen; that in the upper right part of the field shows a solid alveolar grouping, while to the left is an imperfect duct-like structure containing a few red cells in the lumen. The group in the lower part of the field consists mainly of radially-arranged columnar cells. Haematoxylin and eosin. × 300.

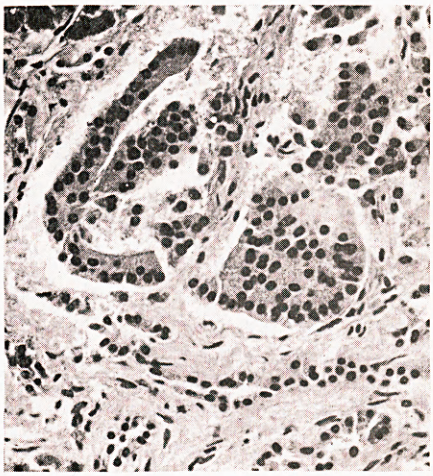

Fig. 6. Case 1. This shows a ribbon-like arrangement consisting of a row of tumour cells; at each end of the ribbon the columnar shape of the cells can be discerned. Haematoxylin and eosoin. ×240.

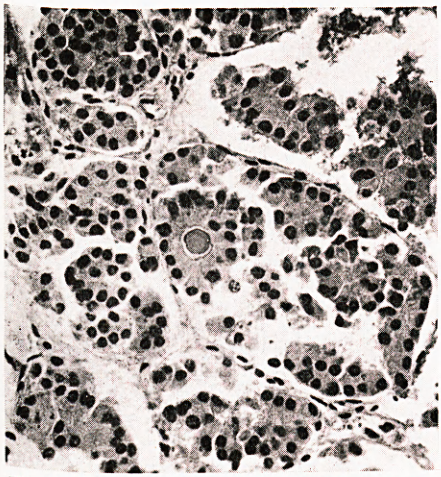

Fig. 7. Case 1. In the centre of the field is a well-formed duct-like structure with the lumen occupied by homogeneous eosinophil material. Haematoxylin and eosin. × 230.

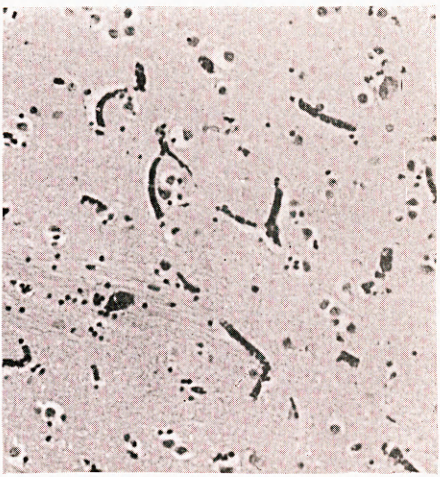

Fig. 8. Case 1. A section of the grey matter of the basal ganglia, showing gross capillary engorgement, and with one small recent perivascular haemorrhage. Phospho-tungstic acid-haematoxylin. × 160.

structures. The individual tumour cells have a single rounded or slightly elongated nucleus with little variation in nuclear size and form ; the chromatin is arranged in fine granules with coarser clumping at the periphery ; usually a single small nucleolus is seen. Mitotic figures are not found.

The cells have a fairly abundant eosinophilic cytoplasm which, in haematoxylin and eosin-stained preparations, presents a ground-glass appearance suggestive of very fine diffuse granularity. The shape of the cells varies with their arrangement ; thus in the solid alveoli, which predominate, the cells are closely applied and polygonal except for the outermost layer of cells in the groups, which tend to be elongated and to form a palisade (Figs. 5 & 6).

In many of the groups of tumour cells, small duct-like structures are seen in transverse section (Fig. 7). The duct wall is formed by a ring of tall columnar cells, often enclosing a small lumen ; the nuclei lie at the base of the cells (away from the lumen). Some of the lumina contain a little granular debris while others are filled with homogeneous eosinophilic material. Red cells are occasionally seen in the lumen, and the question arises whether such structures are merely tumour cells grouped round a central vascular channel ; around the lumina, however, there are neither endothelial lining cells nor reticulin fibrils, and they appear, therefore, to be of a genuine duct-like nature. Many of these structures are less perfectly formed, showing deficiency in part of the wall (Fig. 5), and all gradations are seen between well-formed ducts with a completely enclosed lumen, and elongated ribbon-like bands of columnar cells as seen in Fig. 6. These ribbon-like structures have frequently been described in islet-cell adenomas ; they consist of a single layer of columnar cells with their long axis perpendicular to the long axis of the ribbon, and with the nuclei situated near one edge ; often the ribbon is apposed to one or more layers of polyhedral cells, and the variety of appearances can be attributed to section through various planes of duct-like structures of varying degrees of integrity.

Sections of the pancreas did not show any abnormality in the frequency, size or appearance of the islets of Langerhans. Possibly because of the long interval between death and fixation of the tissues, special staining methods failed to demonstrate specific granulation of the tumour cells, and glycogen was not apparent in suitably fixed pieces of cardiac muscle.

Sections of various parts of the brain showed marked capillary engorgement throughout both the grey and white matter (Fig. 8). There were occasional small recent peri-vascular haemorrhages, especially in the region of the basal ganglia. The nerve cells showed no lesions which cannot be attributed to post-mortem change, and neuronophagia was not seen. No evidence of older haemorrhage nor of gliosis was found.

Two other examples of pancreatic islet-cell tumour associated with hypoglycaemia have been recognized in this hospital in the past few years ; of these, one was admitted in fatal hypoglycaemic coma and the diagnosis was made only post mortem ; this case has already been reported by Stevenson and Rannie (1941) ; the facts of the other case are as follows.

Case 2. A man of 56 presented symptoms suggestive of hypoglycaemic attacks since 1941. The diagnosis of an islet-cell tumour was made, and in 1944 Mr. Scouler Buchanan performed an exploratory laparotomy, but the pancreatic tumour could not be found. In spite of attempts to control the hypoglycaemia by dietary measures the symptoms increased in frequency and severity. In 1946 physical examination showed no abnormality apart from obesity, stated by the patient to be increasing ; the fasting blood-sugar was 40-50 mg. per 100 ml. and the highest level recorded in a sugar tolerance test was 110 mg. per 100 ml., 30 minutes after oral administration of 50 g. of glucose. Typical hypoglycaemic attacks occurred almost daily and sometimes several times in the same day. X-ray of the skull showed no abnormality. Mr. Scouler Buchanan then performed a second laparotomy, and although the pancreas was normal in appearance, palpation revealed a small nodule in the region of the neck of the pancreas, close to the lower border. Incision in this region exposed a small rounded tumour, which was then excised. Recovery from the operation was rapid, and the patient has since remained well with no recurrence of hypoglycaemic attacks. The blood-sugar level rose to 220 mg. per 100 ml. on the first post-operative day, and three days later the fasting level was 100 mg. per 100 ml. A sugar tolerance test performed a fortnight after operation gave a normal result.

Fig. 9. Case 2. Part of the mass of tumour cells interrupted by blood-vessels and numerous cords of hyaline material. Haematoxylin and eosin. × 75.

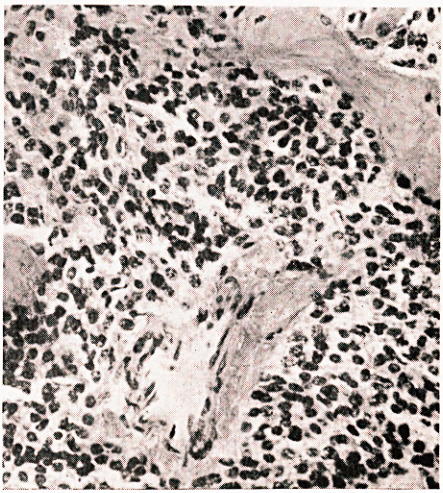

Fig. 10. Case 2. In the lower part of the field a blood-vessel is seen enclosed in a layer of hyaline material, while in the upper right corner, there is an apparently solid hyaline mass. Haematoxylin and eosin. × 240.

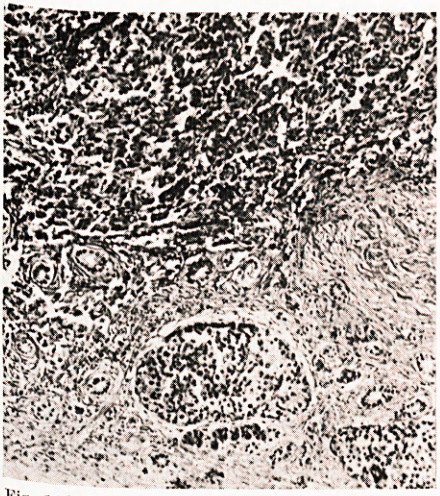

Fig. 11. Case 3. A section from the edge of the tumour showing the fibrous capsule containing scattered ducts and two pancreatic islets; below one of the islets is a small group of pancreatic acini. Haematoxylin and eosin. × 75.

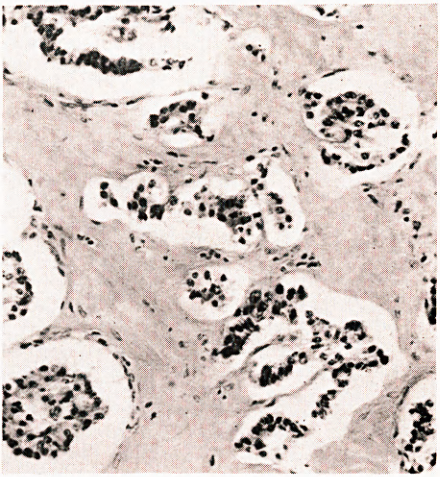

Fig. 12. Case 3. In this part of the tumour there is a coarse fibrous stroma which has largely undergone hyaline change; typical groups of tumour cells are seen lying in spaces in the stroma. Haematoxylin and eosin. × 140.

Histology of the tumour. The tumour was rounded, approximately 1 cm. in diameter, and enclosed in a thin capsule to which a rind of excised pancreatic tissue was adherent. Histologically, the tumour is less well differentiated than that of the previous case; it consists of a solid mass of neoplastic cells, tightly packed and polygonal in shape, with little tendency to form duct-like structures. The cells are not divided up into groups by a stromal network, but the cell mass is penetrated by capillaries and larger vessels. Perivascular deposition of hyaline material is a prominent feature and solid patches of such material are seen where the vascular lumina have been obliterated (Figs. 9 & 10). The cells are similar in appearance to those found in the interior of solid alveolar groups in the previous tumour, but the cytoplasm stains more palely, and it is difficult to discern the cell-outlines. Mitoses are not seen. Special staining methods failed to demonstrate specific granules in the cells of this tumour.

When a pancreatic growth has not given rise to symptoms of hyperinsulinism, it is sometimes difficult to be certain of its nature in spite of histological resemblances to islet-cell tumours, and this is particularly so when the tumour is of long-standing and has undergone extensive hyalinization of the stroma, or where it shows the aberrant characters of malignancy. Nevertheless, non-functioning islet-cell tumours have been described, and the following case is briefly presented as a possible example of a pancreatic tumour of islet-cell type but of the non-functioning variety.

Case 3. The patient, a woman of 47, suffered from peptic ulceration, the symptoms dating over the previous ten years. During that time she had been successfully operated on for perforation of a peptic ulcer, and had had numerous attacks of haematemesis; gastrojejunostomy had been performed but was followed by recurrence of symptoms.

In June, 1947, Professor Illingworth performed a partial gastrectomy with subsequent relief of symptoms. Active peptic ulceration was found in the jejunum adjacent to the gastrojejunal anastomosis and the scars of healed ulcers were present in the first part of the duodenum. An incidental finding was an ovoid retroperitoneal tumour lying just superior to the tail of the pancreas; this tumour appeared encapsulated, and was removed; it had been seen during a laparotomy performed at another hospital five years previously, and did not seem to have increased much in size in the interval.

Histology of the tumour. The tumour was a firm solid ovoid mass measuring 9.5 × 6 × 5 cm., with a smooth surface to which some tags of fatty tissue were adherent. The cut surface presented a mottled appearance, homogeneous pale-yellow tissue alternating with white bands and patches suggesting a coarse fibrosis; the two types of tissue were not sharply defined, but merged gradually.

Microscopy shows the tumour to be enclosed in an irregular fibrous tissue capsule containing pancreatic acini, ducts, and groups of islet-cells (Fig. 11). The tumour itself consists largely of fibrous tissue which has undergone hyaline change; large zones are composed entirely of solid strands of this hyaline tissue, but elsewhere the hyaline stroma is punctuated by spaces containing groups of tumour cells (Fig. 12). These groups of cells show some evidence of duct formation, while ribbon-like structures and solid alveoli are numerous; the individual cells resemble those of pancreatic islets, but show more nuclear aberration than in the previous tumours, and occasional mitoses are present. The presence of pancreatic tissue in the capsule suggests an origin in this organ, while the arrangement and appearances of the neoplastic cells indicate the possibility of an islet-cell nature. The tumour is regarded as being of borderline or low-grade malignant type.

DISCUSSION.

Since the symptomatology in cases of functioning islet-cell tumour is essentially due to hypoglycaemia, it is therefore not surprising that the train of events is similar to that in hypoglycaemia from any cause;

indeed, as mentioned above, the syndrome was predicted on the basis of the insulin overdosage sometimes seen in the treatment of diabetes. Nevertheless the initial symptoms are often misleading and on purely clinical grounds may cause attention to be directed first to other systems. In many cases the presenting symptoms refer to the nervous system, and hypoglycaemia has been mistaken for epilepsy, narcolepsy, intracranial tumour, diffuse disease of the brain and spinal cord, psychosis, and psychoneurosis. In Case 1, the first clinical impression might have aroused suspicions of hysteria, uraemia, or cerebral vascular disease. In this case a noteworthy phenomenon associated with the unconscious state was the reaction of the pupils. The initial pupillary response to light was dilatation. This paradoxical response to light has been noted in various diseases of the nervous system, particularly tabes, general paralysis and midbrain tumours (Duke-Elder, 1949). Such a reaction, however, appears to be rarely observed ; we have been unable to find reference to it in accounts of hypoglycaemic coma, but it was so striking a feature that we wish to draw attention to its presence in this condition. In other cases the presenting symptoms refer to the digestive system and, particularly when gastric hunger contractions are induced two or three hours after a meal and are alleviated by the ingestion of food, duodenal ulcer may be simulated. When hypoglycaemia has been shown to be present, the underlying cause must be ascertained and here the interpretation of blood sugar readings and sugar tolerance tests plays an important part, as Conn (1940, 1947) has emphasized.

An interesting feature of the clinical picture is the irregularity of the occurrence of hypoglycaemic attacks : admittedly the hypoglycaemia is influenced by variations in the carbohydrate intake, but presumably an important factor is the variability in production, or at any rate release, of insulin by the tumour. Thus some cases have attacks of hypoglycaemia occurring daily or more often, with intervening periods of days or even weeks when there are no hypoglycaemic episodes. In this respect an analogy may be made with the phaeochromocytomas which are sometimes associated with intermittent elevation of the blood pressure.

In Case 1, the histological appearances have been described in some detail, as this tumour is a typical islet-cell adenoma. The arrangement of the cells in groups, and the formation of duct-like and ribbon-like structures within the groups is not surprising considering that the islets are developed as outgrowths of epithelium from pancreatic ductules, and that in normal pancreatic ducts occasional islet-cells can be demonstrated (O'Leary & Womack, 1934). The encapsulation and vascular arrangements are also typical of such tumours.

The tumour in Case 2 represents a less well differentiated adenoma, and also shows deposition of hyaline material around the blood vessels ; this hyalinization is a common feature of adenomata which from their

long history of hypoglycaemic attacks may be judged to have been present for several years.

Various authors have been unable to correlate the histological characters of these tumours with their functioning activity. The specific beta granules, usually accepted as being closely linked with insulin formation in normal islets, have been present in only a few cases, while in others atypical granules are evident ; in the majority of cases no specific granules have been demonstrable. Our own attempt to demonstrate specific granules, using the commonly employed staining techniques have been unsuccessful. Early fixation of the material and the use of standardized methods of staining should help, in the future, towards the elucidation of these problems (Gomori, 1945).

A better indication of the functional activity of the tumour may be obtained by biological assay of its insulin content, and Kerwin (1942) and Marble and McKittrick (1946) demonstrated values of the order of between 7 and 100 units per gram, whereas normal pancreatic tissue contains 2 to 3 units per gram.

The pathological changes in the central nervous system in cases which have manifested repeated or prolonged attacks of hypoglycaemic coma are not spectacular and are exemplified by Case 1, where the brain showed only congestion and small perivascular haemorrhages. The effect of hypoglycaemia upon the nerve cells is uncertain and the cytological appearances are often complicated by post-mortem change. Baker and Lufkin (1937) described widespread changes in the neurones, especially loss of Nissl substance. They eventually decided, however, that such changes were of a post-mortem nature, and failed to demonstrate that any changes in the neurones resulted when rabbits were subjected to numerous hypoglycaemic attacks by injection of insulin. They concluded that the nutrition required to maintain the normal structure of nerve cells is less than that necessary for their normal functioning.

Case 2 illustrates some important points in the treatment of functioning islet-cell tumours ; firstly, dietary measures alone do not adequately control the hypoglycaemia : secondly, such small tumours, particularly in obese patients, may be extremely difficult to locate at operation : lastly, it typifies the dramatic cure effected by surgical excision of the offending tumour. The discovery that the administration of alloxan to rabbits resulted in damage to the beta cells of the islets of Langerhans (Dunn *et al.*, 1943) has raised the possibility of destroying islet-cell tumours by the use of this drug (Brunschwig & Allen, 1944). Conn and Hinerman (1948) report a case of functioning islet-cell tumour in which administration of alloxan failed to alleviate the hypoglycaemia ; surgical removal of the tumour was subsequently performed, and was followed by a diabetic condition associated with microscopic evidence of degeneration of the islet of Langerhans closely resembling that produced in rabbits by

alloxan. On the other hand, Bailley (1946) reports an interesting case in which a 9 months old girl with hypoglycaemia presumably due to hyperinsulinism was treated, apparently successfully, with alloxan, after laparotomy had failed to reveal a pancreatic tumour. While alloxan may offer therapeutic possibilities, surgical excision is at present the treatment of choice, affording the only certain means of effecting a cure.

SUMMARY.

A case of fatal hypoglycaemia, associated with an islet cell tumour of the pancreas, is described. Two further cases are briefly reported, one in which hypoglycaemia was cured by operative removal of an adenoma, and the other, a low-grade carcinoma of the pancreas, possibly of islet-cell nature, in which there was no hypoglycaemia. The literature on islet-cell tumours of the pancreas is briefly reviewed.

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