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ORIGINAL ARTICLES

THE INTERNAL SECRETION OF THE PANCREAS*

BY F. G. BANTING, M.B., AND C. H. BEST, B.A.

THE hypothesis underlying this series of experiments was first formulated by one of us in November, 1920,† while reading an article dealing with the relation of the isles of Langerhans to diabetes.[1] From the passage in this article, which gives a résumé of degenerative changes in the acini of the pancreas following ligation of the ducts, the idea presented itself that since the acinous, but not the islet tissue, degenerates after this operation, advantage might be taken of this fact to prepare an active extract of islet tissue. The subsidiary hypothesis was that trypsinogen or its derivatives was antagonistic to the internal secretion of the gland. The failures of other investigators in this much-worked field were thus accounted for.

The feasibility of the hypothesis having been recognized by Professor J. J. R. Macleod, work was begun, under his direction, in May, 1921, in the Physiological Laboratory of the University of Toronto.

In this paper no attempt is made to give a complete review of the literature. A short résumé, however, of some of the outstanding articles which tend to attribute to the isles of Langerhans the control of carbohydrate metabolism, is submitted.

In 1889 Mering and Minkowski[2] found that total pancreatectomy in dogs resulted in severe and fatal diabetes. Following this, many different observers experimented with animals of various species and found in all types examined, a glycosuria and fatal cachexia after this operation. The fact was thus established that the pancreas was responsible for this form of diabetes. In 1884, Arnozan and Vaillard[3] had ligated the pancreatic ducts in rabbits and found that within twenty-four hours the ducts become dilated; the epithelial cells begin to desquamate; and that there are protoplasmic changes in the acinous cells. On the seventh day there is a beginning of

*From the Physiological Department, University of Toronto, Canada.
†F.G.B., then Assistant in Physiology at Western University, London, Ontario.

round-celled infiltration. On the fourteenth day the parenchyma was mostly replaced by fibrous tissue. Sscobolew[4] in 1902 noted in addition to the above, that there was a gradual atrophy and sclerosis of the pancreas with no glucosuria. However, in the later stages, from thirty to one hundred and twenty days after ligation of the ducts, he found involvement of the islets and accompanying glucosuria.

Lewaschew[5] believed that the islets were modified acinous cells. Laguesse,[6] an anatomist, first suggested that the islets might be the organ of pancreatic internal secretion. He showed that there were comparatively more islets in the fetus and the newborn than in the adult animal. Opie[7] and Sscobolew[8] independently furnished the first clinical foundation for the belief that the islets were involved in pancreatic diabetes.

W. G. MacCallum,[9] in 1909, ligated the ducts draining the tail third of the pancreas. After seven months he excised the remaining two-thirds. This was followed by a mild glucosuria. Three weeks later he removed the degenerated tail third. This second operation resulted in an extreme and fatal glucosuria. Kirkbridge,[10] in 1912, repeated and corroborated MacCallum's findings and, by the use of Lane's[11] method of staining, proved that the atrophic tissue contained healthy islets.

Kamimura[12] in 1917, working on rabbits, traced the degenerative changes in the parenchymatous tissue of the pancreas after ligation of the ducts, and found that the islets remained normal and that the animal did not develop glucosuria as long as the islets were left intact.

The first attempt to utilize the pancreas in defects of carbohydrate metabolism was made by Minkowski.[13] This worker tried the effect of pancreatic feeding, with no beneficial results. Up to the present time only useless or even harmful effects have been obtained from repeated attempts to use this method.

Knowlton and Starling,[14] in 1912, published experiments which showed a marked decrease in the power of using sugar of a diabetic heart perfused outside the body, as compared with a normal heart under similar conditions. Macleod and Pearce,[15] using eviscerated animals were unable to confirm the above results. Patterson and Starling[16] subsequently pointed out that a serious error was involved in the early experiments due to (1) excess glycogen present in diabetic hearts, and (2) to the irregular disappearance of glucose from the lungs.

Murlin[17] prepared an alkaline extract of pancreatic tissue and after injection of this solution, secured a reduction in sugar excreted in a diabetic animal. Kleiner[18] has pointed out that the reduction secured by Murlin might be due to the alkali *per se*. Kleiner himself has shown that "unfiltered-water extracts of fresh pancreas diluted with .90 per cent NaCl when administered slowly usually resulted in a marked decrease in blood sugar." There was no compensating increase in urine sugar, but rather a decrease, which Kleiner suggests may be partly due to a temporary toxic renal effect. Hemoglobin estimations made during the experiment showed that the reduction in blood sugar was not a dilution phenomenon. Paulesco[19] has recently demonstrated

the reducing effect of whole gland extract upon the amounts of sugar, urea and acetone bodies in the blood and urine of diabetic animals. He states that injections into peripheral veins produce no effect and his experiments show that second injections do not produce such marked effect as the first.

From the work of the above-mentioned observers we may conclude: (1) that the secretion produced by the acinous cells of the pancreas are in no way connected with carbohydrate utilization; (2) that all injections of whole-gland extract have been futile as a therapeutic measure in defects of carbohydrate utilization; (3) that the islands of Langerhans are essential in the control of carbohydrate metabolism. According to Macleod there are two possible mechanisms by which the islets might accomplish this control: (1) the blood might be modified while passing through the islet tissue, i.e., the islands might be detoxicating stations and (2) the islets might produce an internal secretion.

We submit the following experiments which we believe give convincing evidence that it is this latter mechanism which is in operation.

In the ten-week interval which we considered necessary for complete degeneration of the acinous tissue, we secured records of dogs depancreatized by the Hédon method.[20]

METHODS

The first chart is a record of an animal depancreatized by the Hédon method. The details of this operation are given in Hédon's article.[20] The remaining records are of animals (females) completely depancreatized at the initial operation. The procedure is as follows: under general anesthesia an upper right rectus incision is made through the abdominal wall. The duodenum is delivered through the abdominal wound, and the pancreas traced to the tail portion. The mesentery beyond is cut between clamp and ligature. Vessels from spleen are then isolated, ligated and divided. Little dissection is then required until the duodenum is reached. The superior pancreatico-duodenal vessels are located and great care is exercised to avoid damaging them. The pancreas is stripped from the duodenum by dry dissection. The vessels to the uncinate process are ligated and divided, and the process freed from its mesenteric attachments. The larger duct of the pancreas is then ligated close to its entry into the duodenum and the pancreas is removed. Special care must be exercised to preserve the splenic vessels. The superior pancreatico-duodenal vessels must be left intact. Failing this, duodenal ulcer is a frequent development. If this procedure is carried out the whole gland with the exception of the portion in contact with the duodenum is covered with mesentery. The abdominal wound is closed layer by layer with catgut. A collodion dressing is used. The urethral orifice is exposed by a midline incision of the perineum and the edges of the wound drawn together to facilitate healing.

We have found that animals between eight and sixteen months old are the most suitable for this operation. At this age the pancreas is not so firmly fixed as it becomes later.

We first ligated, under general anesthesia, the pancreatic ducts in a

number of dogs. (Blood sugar estimations on these animals were recorded from time to time. We have no record of a hyperglycemia).

The extract was prepared as follows: The dog was given a lethal dose of chloroform. The degenerated pancreas was swiftly removed and sliced into a chilled mortar containing Ringer's solution. The mortar was placed in freezing mixture and the contents partially frozen. The half frozen gland was then completely macerated. The solution was filtered through paper and the filtrate, having been raised to body temperature, was injected intravenously.

We have never found it necessary to cut down on a vein under general or local anesthetic. The skin surface above the vein is shaved and the needle inserted into the vein which is dilated by compression. The dogs make very little resistance to this procedure and after the first few punctures lie quietly during the operation. Sugar injections (100 c.c. of fluid) as well as the numerous administrations of extract were conducted by this method.

We performed several experiments with the object of exhausting the zymogen granules of the pancreas. Prolonged secretin injections and vagus stimulation below the diaphragm were practiced. Fortune favored us in the first experiment. In subsequent attempts we were never able to exhaust the gland sufficiently to obtain an extract free from the disturbing effects of some constituent of pancreatic juice.

The blood sugar estimations were made by the Myers-Bailey[21] modification of the Lewis-Benedict method. The results of this method were corroborated by the Schaffer-Hartman[22] method at high and low percentages of blood sugar. The former method gave results which were consistently slightly higher (.01 per cent) than those obtained by the Schaffer-Hartman method. We find the average normal blood sugar, from observations on thirty normal dogs, to be .090 per cent.

Hemoglobin estimations were made by the carbon-monoxide saturation method, using the du Bosq colorimeter.

RESULTS

Chart 1 contains the record of a 6.5 kilogram dog (410). This experiment is not conclusive but is interesting to us at least, since we administered the first dose of extract of degenerated pancreas to this animal. On July 11, the pancreas, with the exception of the processus uncinatus, was removed. The processus was allowed to remain until July 18. In the interval between the operations there was no hyperglycemia or glucosuria. The curves on subsequent days show the effect produced by the removal of the pedicle. It will be noted that as the experiment progresses the percentage of blood sugar did not rise to the level usually attained in completely depancreatized animals, and also that there was a marked decrease in the daily amounts of nitrogen and sugar excreted and the volume of urine voided. The animal continued to lose weight and seemed to be entering the cachexial condition characteristic of depancreatized animals which had become infected.

The chart for July 27 shows the effect produced on the percentage of

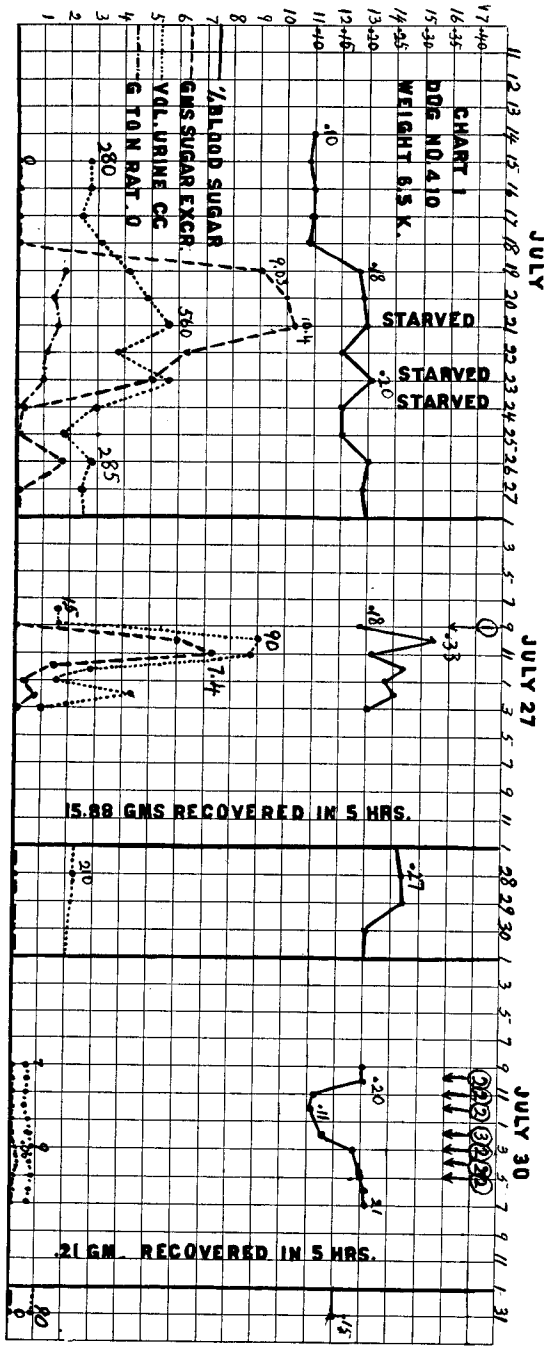

Chart 1.—(1) 25 gms. glucose in 250 c.c. water by stomach tube. (2) Degenerated gland extract, 5 c.c. dose intravenously. (3) .20 gms. glucose in 200 c.c. water by stomach tube. Dog died July 31st—cachexia.

blood sugar and on the sugar excretion by the oral administration of twenty-five grams of dextrose in two hundred and fifty c.c. of water.

At 10 A.M. July 30, the percentage of blood sugar was 0.20. Four c.c. of extract of degenerated pancreas were injected intravenously. At 11 A.M. the blood sugar had fallen to 0.12 per cent. The injections of extract are shown

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