REGENERATION OF PANCREATIC TISSUE FROM THE TRANSPLANTED PANCREATIC DUCT IN THE DOG

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Regeneration or extensive new growth of the pancreatic duct has been reported by Fisher (1924b), and regeneration of pancreas tissue (acini and islets) from the pancreatic duct tissue have been reported by several investigators, Languesse and de la Roche (1902), Cecil (1911), Bensley and Clark (1914). These observations deal with regeneration of pancreas from duct tissue left in situ, such as follows complete occlusion of the pancreatic ducts. Fisher (1924a) reported from this laboratory regeneration of a considerable mass of pancreas tissue from duct stump left in the duodenal wall in the operation of complete pancreatectomy. These two dogs were controlled by insulin. We have also reports of histological evidence of regeneration of new islets from the duct system in some cases of diabetes in man (Weichselbaum, 1908; Boyd and Robinson, 1925). But Bensley, in discussing the paper by Boyd and Robinson, points out the uncertainty in the interpretation of the histological findings in the pancreas of human diabetics.

The work here reported was undertaken at the suggestion of Doctor Carlson, on the following working hypothesis: There is experimental evidence that in normal animals the pancreatic duct can produce islets and acini, at least under some experimental conditions. Assuming an essential pancreatic factor in human diabetes, significant regeneration of islets must be absent or extremely rare, because significant recovery of carbohydrate tolerance even under insulin and dietary control is, at present, exceptional. This apparent failure of pancreas duct tissue to produce new islets may be due to a, congenital defect in growth potential of the pancreas; b, toxic injury of both islets and duct systems; or c, continuous injury (toxic) of the islets newly formed from the ducts. If the first hypothesis is a factor, transplantation of the pancreatic duct might be of value, provided a duct transplant takes and produces islets.

METHODS. Segments of the pancreatic duct, completely freed from pancreas tissue, were implanted under the serosa of the duodenum in dogs,

1 This work was started in 1923 by Mr. Shaw, who completed the experiments on dogs 1 and 2. The experiments on dogs 3 to 7 were carried out by Mr. Latimer. I have checked their findings and combined their reports.—A. J. C.
at the time that complete or partial pancreatectomy was performed. The
dogs were subsequently controlled by insulin, so that the urine remained
nearly free from sugar. Pieces of the duct, varying in length from 1 to
2 cm., were used. The duct segments were pulled under the serosa by a
cutting needle. No stitches were taken in the graft.

RESULTS. 1. Completely pancreatectomized dogs. Dog 1. Female
weighing 10.5 K. Pancreatectomy and duct transplantation, November 6,
1923.

The dog continued to lose weight for a week, reaching 8.5 kilos where she
remained throughout the experiment. The urine was kept sugar-free with
25 units of insulin twice a day for the first month, 20 units twice a day for
the next three months, and 25 units once a day for the last month of life.
One hundred sixty-two days after operation the dog died suddenly from
undetermined cause. At autopsy there was found at the site of transplant
a small piece of tissue about 1 cm. in diameter. The rest of the duodenum
was entirely free from pancreatic tissue. This tissue was removed, placed
in Zenker's solution, sectioned and stained with hematoxylin and eosin.

Microscopically the tissue is composed of small lobules associated with
lobes. The lobules are united by a delicate and relatively loose fibro-
elastic connective tissue. Numerous and varying sized ducts are seen.
The inter-lobular ducts are lined by a single layer of columnar cells. The
intercalary ducts terminate by passing into the acinus. The acinar cells
are tall and irregularly columnar or pyramidal in shape. In addition to
the above there are certain larger and smaller spheroidal collections of
polyhedral cells which lie in the inter-acinar connective tissue, determined
to be islands of Langerhans.

Dog 2. Weight 12 kilos. Prepared as dog 1. At no time did this
dog show any tolerance to sugar, needing approximately 45 units of insulin
a day throughout the experiment to keep the urine sugar-free. The dog
died of pneumonia 72 days after the operation. At autopsy the duodenum
was free from pancreas tissue. The duct transplant was recovered and
prepared for microscopic study. The main duct was lined with a single
layer of high columnar cells, surrounding this main duct were numerous
smaller tubules lined by a single layer of cuboidal cells which in serial
section were found to be connected with this main duct. There was no
definite evidence of acinar or islet tissues, but duct lived and smaller ducts
had developed from the original transplant.

Dog 3. Female weighing 8 kilos. Operation June 6, 1925. All traces
of glandular tissue were removed from the ligated duct stump to see
whether the duct stump in situ would regenerate glandular tissue. Three
implants of the main duct were made under the serosa of the jejunum.
The urine was kept sugar-free by means of insulin. The wound healed
rapidly, and the animal was in good condition until three days before its
death, August 3, 1925, fifty-eight days after the operation. The cause of death was pneumonia. At autopsy the transplants were found. They contained a clear fluid. At the duct stump, between the ligature and the gut, was a piece of tissue weighing 0.3 gram and grossly resembling glandular tissue. Microscopical examination of the transplant showed it to be living and to have formed a great many small tubules, but no definite acini or islets. Microscopical study of the tissue taken from the duct stump showed it to be composed partly of fibrous connective tissue and partly of newly formed pancreas tissue containing both acinar and islet formations.

2. Partial pancreatectomy. Dog 4. Male, weighing 9.4 kilos. Operation, January 17, 1925. Transplants of both the main and the accessory ducts were made under the serosa of the jejunum. The animal died of pneumonia February 9, 1925, twenty-three days after the operation. Both transplants were recovered. Microscopically they were found to be living and to have begun to proliferate new tubules. No distinctly glandular tissue was present.

Dog 5. Male, weighing 14 kilos. Operation, April 16, 1925. The operation consisted in an almost total pancreatectomy; a piece of glandular tissue about the size of a pea being left attached to the duodenum. Three implants were made of the main duct, and one of the accessory duct, all under the serosa of the duodenum and jejunum. For twelve days from eight to twenty-four units of insulin were required to keep the urine sugar-free, but after the twelfth day no insulin was required. The animal recovered rapidly from the operation, gained weight, and remained in perfect health. The dog was etherized June 30, 1925, seventy-five days after the operation. At autopsy three of the transplants were recovered. Each of the transplants was filled with a clear fluid. Microscopical study of the transplants showed that they were living, and that many small tubules had been formed, with indication of regenerating some gland cells.

Dog 6. Male, weighing 7.5 kilos. Operation, May 1, 1925. Three transplants of the main duct were made under the serosa of the ileum. The animal recovered slowly from the operation, but after recovery remained in very good health. The dog was etherized July 15, 1925, seventy-six days after the operation. At autopsy the three transplants were recovered. Each transplant was filled with a clear fluid. Microscopical study of the transplants showed them to be living and to have proliferated with the formation of many small tubules, probably with the regeneration of some glandular tissue.

Dog 7. Male, weighing 8 kilos. Operation May 15, 1925. Three transplants were made of the main duct under the serosa of the duodenum and jejunum. The animal made a rapid recovery and was in good health throughout the experiment. It was etherized July 15, 1925, sixty-one days
after the operation. At autopsy all the transplants were recovered. Each transplant was filled with a clear fluid. Microscopical examination of the transplants showed them to be living, with the formation of many small tubules, and probably with regeneration of some glandular tissue.

**Discussion.** The objection might be raised to these experiments that not all of the glandular tissue had been removed from the duct prior to transplantation. But in cases of six animals autopsied from six to fourteen days after the transplantation, no traces of glandular tissue was found. Therefore we feel safe in concluding that the regeneration we have observed came from the duct tissue.

Fisher (1924a, b) failed to observe any regeneration in his duct transplants, but the longest he carried his experiments was forty-two days. Since all of the transplants carried over fifty-eight days showed the formation of many small tubules and indications of regenerated glandular tissue, and since transplants carried less than fifty-eight days showed no evidence of regeneration, it is quite obvious that the time factor is very important in the regeneration of pancreatic tissue from a transplanted duct. Further, the fact that the above-mentioned time factor operated in both totally and partially pancreatectomized dogs shows that the time factor is much more important than the diabetic factor.

The presence of the fluid in the ducts (dogs 5, 6, 7) suggests that there had been a regeneration of acinar cells but that these had degenerated some time prior to the autopsy because the secretion did not find an exit. The cells of the duct are not known to have a secretory function, but we do know that on ligation the pancreatic duct the acinar cells degenerate. The regeneration of the glandular tissue from the duct stump corroborates Fisher's findings. This tissue, as in Fisher's case, had a drainage into the gut. This indicates that in the transplants regeneration of pancreas tissue occurs in all probability more rapidly and completely after the duct has established connection with the lining of the intestine.

**Conclusion**

In completely or partially pancreatectomized dogs (the diabetes being controlled by insulin) homografts of the pancreatic duct in the intestinal wall become vascularized and undergo varying degrees of differentiation or regeneration towards pancreas tissue. In one case (dog 1) a small mass of acini and islets was found regenerated from the transplant 162 days after the transplantation. In all of the experiments prolonged for two months or more regeneration of ductlets was always in evidence, with some indications of acini and islet formation. When the transplanted and regenerating duct does not establish connection with the lumen of the gut, secretion accumulates in the ducts. This factor probably retards the regeneration of pancreas tissue. Operative methods facilitating such duct-gut con-
nection would probably yield more positive results than those obtained in the present work.

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