ENDOCRINE FUNCTIONS OF THE PANCREAS

BERNARD ZIMMERMANN, M.D.

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By

BERNARD ZIMMERMANN, M.D.

Department of Surgery
University of Minnesota
Minneapolis, Minnesota

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WILLARD O. THOMPSON, M.D.
Clinical Professor of Medicine
University of Illinois College of Medicine
Managing Editor
Journal of Clinical Endocrinology
Chicago, Illinois

TO MY FATHER

Skillful surgeon, original thinker, wise counselor

PREFACE

As in every field of medicine, the surgical and medical treatment of diseases of the pancreas has advanced to a point from which further progress is dictated almost entirely by the basic contributions of physiologists and biochemists. It was in view of this that it seemed worthwhile to collect such past and recent physiological information as might be pertinent to the further understanding of clinical situations in which the pancreas plays a part. The experimental literature dealing with the pancreas as an endocrine organ is vast, and although a considerable amount of bibliographic material has been cited, this review is far from exhaustive. The bibliography included here must be considered only an introduction to this absorbing field of scientific literature.

Many of the most significant questions considered here have been the basis of heated divergences of scientific opinion. Some of these controversies, which have lasted for decades, remain unsettled at the present time. In dealing with these problems, I have tried to present some of the data on each side of the arguments. Where final conclusions can not yet be reached, the experimental facts, at least, should be known to us.

The book would be incomplete without the expression of my profound gratitude to four men with whom it has been my privilege to be associated during the past seven years and who have made it possible for me to pursue my interest in the pancreas. They are Dr. Edwin B. Astwood of Boston, Captain Albert R. Behnke and the late Captain Erik G. Hakansson of the Naval Medical Research Institute, and Dr. Owen H. Wangensteen of the University of Minnesota.

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BERNARD ZIMMERMAN

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ENDOCRINE FUNCTIONS OF THE PANCREAS

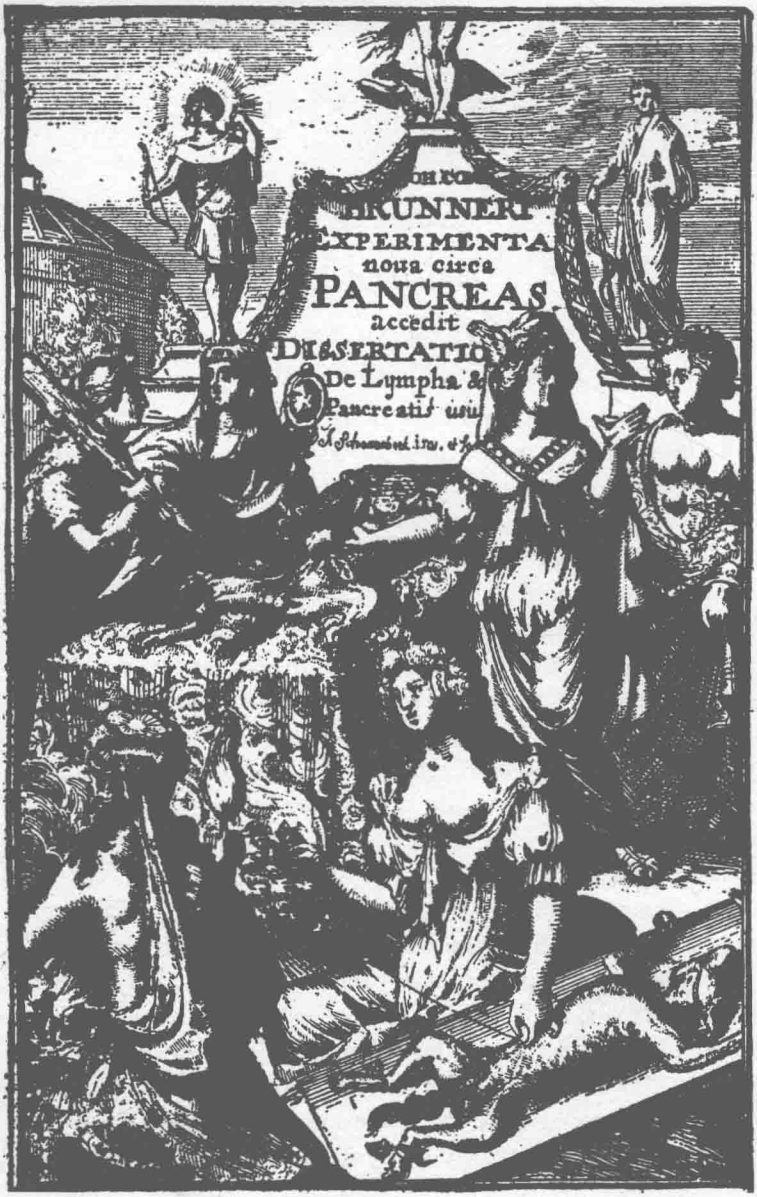

FIG. 1. Frontispiece from Brunner's *Experimenta nova circa Pancreas* depicting the operation of pancreatectomy being carried out in dogs. The operations are being performed by six ladies, and the importance of the experiment is signified by the presence of Aesculapius, Eros, and Zeus (or possibly, Prometheus) at the demonstration. For further discussion see Major, H. H.: *Ann. Med. History, 3:*91 (1941).

CHAPTER I

HISTORY

THE PANCREAS AS AN ORGAN OF INTERNAL SECRETION

THE first suggestion that diabetes mellitus might be related to the impairment of some function of the pancreas is believed to be that contained in a case report written by Thomas Cawley in 1788 (11). In this interesting and thoughtful report the author described a case of severe, rapidly progressive diabetes which terminated in characteristic diabetic coma. An autopsy disclosed extensive pancreatic lithiasis with sclerosis and atrophy of the pancreatic tissue. Cawley reviewed the theories of diabetes which existed at his time. There were two general schools: one which believed the liver was the organ primarily affected in diabetes and a second which held that the kidneys were the seat of the disorder. After discussing these theories Cawley concluded that neither applied to his case and suggested that the disease of the pancreas in this instance was the primary pathologic process which had produced the metabolic disturbance.

Experimental pancreatic diabetes: Although clinical diabetes associated with gross lesions of the pancreas is a relatively rare picture even today, enough cases similar to that of Cawley were observed during the course of the next hundred years so that the relationship of the pancreas to diabetes was suspected by many investigators. In 1877 Lancereaux reviewed these cases, adding two from his own experience, and stated definitely his opinion that in at least some cases of diabetes the primary disease was in the pan-

creas (20). Experimental evidence for this relationship was lacking until 1889 when von Mering and Minkowski in Strassburg succeeded in producing characteristic diabetes mellitus in the dog by total extirpation of the pancreas (27).

Although von Mering and Minkowski were the first to recognize the presence of diabetes in the depancreatized animal, the operation had been attempted by many earlier investigators. As early as 1682, Conrad Brunner, the discoverer of the duodenal glands which bear his name, had successfully removed the pancreas from dogs and described his experiments in a book entitled *Experimenta Nova circa Pancreas atque Diatribe de Lympha* (10). The cryptic frontispiece to this little book depicts the pancreatectomies being carried out (Fig. 1). Whether Brunner actually produced diabetes in any of his animals will, of course, never be known, but one is led to believe that he did by the following description of one of his dogs from which he had removed both spleen and pancreas.

> It was especially to be seen that the animal made water very frequently, and that he was very thirsty, drinking largely of water in proportion to the discharge of urine.

Unfortunately, the author was not stimulated to investigate these observations further since he knew Malpighi had described excessive thirst in animals in which he had only ligated the splenic vessels (15). Subsequent investigators before von Mering and Minkowski apparently failed to accomplish complete removal of the pancreas, and in 1856 Claude Bernard stated that it was impossible to perform total pancreatectomy in the dog (8). He did carry out the operation in birds and though the situation so produced was not consistent with prolonged life, the symptoms of diabetes were not seen (9).

The experiments of von Mering and Minkowski were repeated by Lépine who first proposed that the pancreas ex-

erted its anti-diabetic function through the activity of an internal secretion (24, 23). Conclusive proof of this concept was provided by the subsequent experiments of Minkowski and of Hédon who demonstrated that if the entire pancreas were removed except for a small subcutaneous graft, there was no metabolic impairment, but when the graft was excised, the typical diabetic picture appeared within a few hours (28, 16). This was almost incontestable evidence for the endocrine theory.

The islets of Langerhans: Diamare in 1889 and Laguesse in 1893, on the basis of histological and embryological studies, postulated that the endocrine tissue of the pancreas consisted in the nests of epithelial cells which had been described by Langerhans in 1869 (22, 19, 12). It was Laguesse who proposed the name "Les Îlots de Langerhans" for these structures. That the islets were the source of the internal secretion became accepted on the basis of the work of Ssobolew and others who injected the pancreatic duct system with paraffin (29). While this procedure effected very complete destruction of the acinar elements which became replaced by fibrous tissue, the islets were unimpaired and diabetic symptoms did not appear.

The apparent importance of the islets of Langerhans as an endocrine system stimulated further anatomical research as a result of which it was shown by Bensley and Lane that various methods of staining delineated more than one type of islet cell (21, 7). The most numerous were found to be two granulated types referred to by Lane as A and B cells. The alpha cells, as they are now called, are the less numerous of these types and tend to be located peripherally in the islet. In addition to these two prominent forms there are "D" cells and a fourth non-granular "C" cell which was described by Bensley in the guinea pig.

There is adequate evidence that the beta cells are the

source of insulin. Early experiments dealing with the exhaustive degeneration of the islets which follows subtotal pancreatectomy showed that it was the beta cells which became damaged in this process (21). More recent observations of the pancreas in pituitary and alloxan diabetes have yielded similar findings (Chapter V).

The discovery of insulin: During the thirty years which followed the experiments of von Mering and Minkowski innumerable attempts were made to prepare extracts of pancreas with anti-diabetic activity. There is little doubt that many of these earlier investigators did obtain extracts with hypoglycemic properties. The preparations were either too toxic or insufficiently potent or the methods for evaluating them were not adequately refined so that no convincing results were achieved before the work of Banting and Best in 1921 (3). Sir Frederick Banting had conceived the idea for his experiments after reading an article by Moses Barron concerned with the degenerative changes in the human pancreas which follow occlusion of the ducts by calculi (6). Banting and Best ligated the pancreatic ducts of dogs, allowed enough time for the acinar tissue to degenerate, and then removed the atrophied pancreases and extracted them with cold Ringer's solution. Extracts thus produced possessed striking ability to lower the blood sugar of depancreatized animals (3). The use of degenerated pancreas avoided the introduction of toxic pancreatic enzymes into the recipient animals and probably prevented some enzymatic destruction of the insulin. This aspect of their procedure, however, was probably not alone responsible for the success of these workers where others had failed. The use of more accurate methods for blood sugar determinations and the more frequent withdrawal of blood samples for analysis contributed significantly to their success.

Following the preparation of insulin from the sclerosed pancreatic remnants, Banting and Best found that similar