were, it would constitute an additional factor in this organ's physiological functions.

To which of the two pancreatic active structures can we hypothetically ascribe the formation of the glycolytic enzyme? Laguesse[35] has ascribed this function to the islands of Langerhans. That these structures underlie some physiological process in addition to that already analyzed by us is undoubted. The fact that they contain large nuclei shows that they are physiologically active. "The cells composing the islands resemble those of the acini," says Opie; "they have a large, round, occasionally oval, vesicular nucleus and a conspicuous cell-body." They must produce some ferment or its zymogen, for Ssobolew found that feeding animals on carbohydrates caused them—*i.e.*, their protoplasm—to become granular. This is indirectly confirmed by the fact that these bodies are often found diseased in diabetes. They had entirely disappeared in two of Ssobolew's cases. In a case of Opie[36] hyaline metamorphosis was strictly limited to the islands of Langerhans the glandular acini remaining intact. Flexner[37] refers to this cause of diabetes as follows: "That it depends upon an internal secretion supplied by the pancreas to the blood is highly probable. Whether this hypothetical secretion is the product of the cells of the islands of Langerhans is unproven."

The data bearing upon this source of diabetes are very few,—an unfortunate fact, since these particular structures seem to us to play the predominating rôle in the production of glycosurias of pancreatic origin, now that we have ascertained that they are, through their ampullæ, the only thoroughfares for the splenic ferment. Still, can we, with Laguesse, now consider them as the source of a glycolytic ferment? Were we to admit this possibility, we would find ourselves obliged to concede that the pancreas supplies the intestinal tract with a glycolytic ferment besides an amylolytic ferment, and we would have, as a result, the formation of maltose from food-starches and its immediate destruction by the glycolytic ferment, thus annulling the very important functions of sugar in the economy.

[35] Laguesse: *Loc. cit.*
[36] Opie: Journal of Experimental Medicine, March 25, 1901.
[37] Flexner: University of Pennsylvania Medical Bulletin. Jan., 1902.

It is plain that the islands of Langerhans are not the source of a glycolytic ferment. Of course, Professor Lépine has never, that we know of, sustained this view, his contention being simply that the normal pancreas contains a glycolytic ferment which finds its way into the lymph and blood, in which it controls the consumption of sugar by the tissues. And his experimental evidence, in the light of our views, shows this to be the case, since it all goes to prove that the oxidizing substance which enters the pancreatic circu'ation is a glycolytic body. This does not mean that it acts therein as such; indeed, the organic cells at once take up its oxygen for their own functional interchanges, the blood returning to the splenic veins as venous blood. But it is nevertheless obvious that Lépine should have experimentally found, as he says, a glyco'ytic ferment in the pancreatic blood. All we show, therefore, is that Lépine's glycolytic ferment is probably the oxidizing substance.

But why should disease of the pancreas under these circumstances increase the proportion of sugar in the urine: a feature which Lépine ascribed to decrease of sugar destruction and to the fact that "these lesions decrease the source of the glycolytic ferment in the economy"? From our standpoint, of course, the adrenals are the original source of the oxidizing substance: *i.e.*, adrenal secretion *plus* oxygen. But does this account in an equally satisfactory manner for glycosuria? This introduces a very important feature of the entire analysis, one, indeed, bearing upon the pathogenesis of all forms of pancreatic diabetes.

We have previously referred to the fact that disease of the islands of Langerhans had been found to be a prominent causative factor of diabetes by various pathologists, and that Opie had witnessed a case in which these islands *alone* were diseased. This obviously points to the fact that, *if in accordance with our view the ampullæ of the islands are the pathways of the Schiff-Herzen splenic substance to the ducts,* we are dealing either with obstruction or impaired conversion of trypsinogen into trypsin, or both simultaneously. If, bearing this feature in mind, we review the list of pancreatic diseases that cause

glycosuria, it will become apparent that these two factors account for the phenomena observed in many cases: calculi, lipomatosis, hypertrophy, tumors, induration, and periglandular sclerosis. Atrophy,—a condition which in itself implies functional impairment,—on the other hand, constitutes the majority of the remaining pathological processes encountered post-mortem in this organ.

But the question which now imposes itself is this: Why and how does a condition that interferes with the conversion of trypsinogen into trypsin or that impedes the passage of the latter to the intestinal foodstuffs cause diabetes? The answer now seems plain, viz.: *because insufficiency of trypsin is followed by imperfect reduction of proteids to simpler bodies, resulting in the formation, or inadequate splitting, of toxic albuminoids.* In other words, impaired pancreatic action of the kind mentioned gives rise to toxic glycosuria.

Our interpretation of the general subject seems again to conciliate antagonistic views. Indeed, while Lépine[38] has affirmed that "the pancreas exercised a glycolytic influence," Chauveau and Kaufmann have held the opposite: *i.e.*, that "glycolysis is not diminished in diabetes, and that diabetes is exclusively due to an increase in the production of glucose." We have shown that the arterial blood of the pancreas does contain a glycolytic body,—the oxidizing substance,—but we have also—by our analysis of Cartier's paper and other data—demonstrated that suprarenal overactivity was the underlying cause of toxic glycosuria: *i.e.*, a source of increased production of sugar. To further sustain this fact, we may recall that the coal-tar products, as already stated, possess a marked tendency to inhibit the functions of the adrenals, sufficiently, in some instances, to produce blood-disintegration. Lépine has himself observed that methæmoglobinuria could follow the use of antipyrin. This remedy is now classed among the most active agents at our disposal for the reduction of glycosuria. A remark of Professor Lépine proves this to be the case in another way. Referring to experiments conducted with the collaboration of Porteret, he says, regarding the action of

[38] Lépine: "Le Diabète," Paris, 1899.

antipyrin, that, "in the cases in which it exercises an antidiabetic action, this substance acts, not by activating the destruction of sugar, but *by preventing its formation.*"[39] This is due, as explained in the second volume, to the fact that antipyrin excites a center (the sympathetic center, also described in the second volume) whose purpose is to cause constriction of the arterioles after, as we have seen, they have been dilated by a cranial nerve. Antipyrin thus produces general constriction of the arterioles, and the blood admitted into the adrenals, pancreas, and liver—the main organs involved in diabetes—being reduced, the "formation" of sugar is actually prevented.

In view of these facts, what is the nature of the product the existence of which the prominent nuclei and the granules observed in the protoplasm of the islands indicate? This is elucidated by two other features just brought out, namely: (4) that glycosuria may be the result of intoxication by toxic albuminoid bodies incident upon an insufficiency of trypsin, and (5) that disease limited to the islands, as shown by Opie, can cause glycosuria. It is plain that, in the latter case, the permeability of the ampullæ being alone compromised, the pancreatic lobules that contain no islands are free as to the elimination of their secretion into the ducts. If they produce trypsinogen,—*i.e.*, trypsin,—why are the functions of the latter inhibited or absent as indicated by the glycosuria? The only logical answer to this question is that *the islands of Langerhans alone secrete trypsinogen.*

This fact, when added to others reviewed, normally leads to another deduction: *i.e.*, that, in addition to any other function it may possess, *the spleen and the islands of Langerhans are functionally united in the formation of a ferment,—trypsin,—which is able to digest albuminoid bodies in the blood-stream.*

We can now readily understand why the spleen and the pancreas are so intimately connected through their nervous supply. Indeed, this throws light upon a phenomenon which we approach almost with diffidence: *i.e.*, Claude Bernard's experimental glycosuria obtained by puncturing the medulla oblongata. "That pathological conditions of the central nerv-

[39] The italics are Professor Lépine's.

ous system and perhaps of the sympathetic and larger peripheral nerves may give rise to glycosuria and diabetes is, of course, established," says Flexner.[40] "The number of neuropathic conditions in which one or the other of these has been found is now considerable. The one definite condition, *the effect of which is constant,* is Claude Bernard's *piqûre,* and, as bearing out the physiological relationship existing between *certain unknown structures* in the floor of the fourth ventricle and the glycogen-store in the liver, may be cited the instances of lesions (hæmorrhages, softening, tumors) in man observed in this situation with which glycosuria has been associated. That cerebral and perhaps spinal disturbances other than those in the region of the fourth ventricle may be associated with or followed by diabetes many clinical cases prove. On the other hand, there is no evidence that would show that it is the direct influence of the central nervous system upon the carbohydrate metabolism that produces hyperglycæmia and glycosuria. Indeed, the experiments in which *the splanchnics were sectioned after piqûre* (Claude Bernard and others) *without producing glycosuria* show the necessity of the interaction of other organs."[41]

Read in the light of all we have said,—particularly the allusion to the relationship between the medulla and the suprarenal glands through the splanchnic,—these lines, from so competent an observer as Flexner, and which confirm those of Cartier as to the action of section of the splanchnic, seem to us to afford confirmatory evidence based upon the most sclid labors of the last half-century and to embody Claude Bernard's own sanction. To analyze their far-reaching meaning would involve the repetition of what has been said in all this volume. Formulated as a deduction, the functional relationship between the floor of the fourth ventricle and glycosuria would be as follows: *Puncture of the floor of the fourth ventricle (Claude Bernard) causes glycosuria because the increased blood-supply in the injured area incident upon the local reparative process correspondingly excites the normal structures around this area. As*

[40] Flexner: *Loc. cit.*
[41] All italics are our own.

these structures include nerve-fibers which govern the adrenals, these organs are stimulated and glycosuria is produced by their secretion.

What we might term the intrinsic functions of the pancreas have now been analyzed; the importance—also in conjunction with the spleen—of its *extrinsic* functions must now be inquired into. Foster states that "a pancreas taken fresh from the body, even during full digestion, *contains but little ready-made ferment,* though there is present in it a body which, by some kind of decomposition, *gives birth to the ferment.*[42] . . . To this body, this mother of the ferment, which has not at present been satisfactorily isolated, but which appears to be a complex body, splitting up into the ferment, which, as we have seen, is, at all events, not certainly a proteid body, and into an undeniably proteid body, the name of *zymogen* has been applied. But it is better to reserve the term zymogen as a generic name for all such bodies as, not being themselves actual ferments, may by internal changes give rise to ferments, —for all 'mothers of ferment,' in fact,—and to give to the particular mother of the pancreatic proteolytic ferment the name trypsinogen." In other words, and in accord with prevailing custom, each zymogen is named from the ferment it produces: the zymogen of trypsin being "trypsinogen"; that of pepsin, "pepsinogen," etc. It is therefore permissible to use the term "amylopsinogen" as the main product of the true lobular acini to differentiate it from trypsinogen, the product of the islands of Langerhans, reserving the term zymogen as a generic term for all pancreatic ferments. As "zymogen" under these conditions, it preserves characteristics attributed to it by Heidenhain; it is soluble in water, in which it is split, after exposure to the air, into trypsin, etc. (Charles). The conversion of trypsinogen into trypsin has been ascribed to oxygen; but if my views are sound and the former is the normal product of the islands, the portion distributed through the pancreatic ducts is intimately combined with the splenic ferment in the ampullæ as fast as formed, so that it can never be obtained as trypsinogen. Hence, oxygen will split zymogen into trypsin, etc.; but trypsin is not oxidized trypsinogen.

[42] The italics are the author's.

We have followed the course of the blood from the splenic vein and back again to the splenic artery which supplies branches to the pancreas, and we have seen that on its way through the latter the arterial blood surrenders its oxygen to the cells and its splenic substance to the islands. The dominant feature of the extrinsic functions of the pancreas is its power to destroy albuminoid toxic bodies, and it is evident that the splenic ferment, the mission of which is merely to unite with trypsinogen to form trypsin, cannot do this alone. It is *trypsin* that constitutes the antitoxic body, and it is the pancreas, therefore, that supplies it to the organism. How does it penetrate the general blood-stream?

Now that we have ascertained that the islands of Langerhans are the seat of manufacture, as it were, of at least a part of this antitoxic agency, and that it collects (combined) in the ampullæ, the manner in which the general circulation becomes supplied with it is clear: *i.e.*, the quantity that permeates through the ampullar walls is but a portion of their contents, and the rest is swept away with the blood and reaches the splenic vein through the pancreatic veins. But this does not mean that trypsinogen may not be carried alone in the same manner to the splenic vein and therein combine with the splenic ferment to form trypsin. In fact, this must constitute the prevailing process, if the anatomical distribution of the islands of Langerhans, as observed by Opie, can serve as guide.

As we have seen, Opie found that the islands of Langerhans were over three times as numerous in the splenic end of the pancreas as elsewhere, and that the part of the organ not in communication with the splenic vein—*i.e.*, the extremity of the descending arm—contained none. Moreover, each lobule in the splenic end of the organ was found to contain an island: a very suggestive fact. The tip of the pancreas, which is almost in contact with the spleen, thus marks the starting-point of the islands; so that trypsinogen begins to enter the splenic vein almost at the hilum. Pancreas and splenic vein being connected by several short venous radicles at about regular intervals, the blood in the vein must become literally saturated with trypsinogen, and its blood be replete with trypsin when it reaches the portal vein, during the active stage of

intestino-portal digestion. We have seen in Herzen's experiment how rapidly albumin was digested with blood obtained from the splenic vein during this stage.

That the amylolytic ferment derived from Heidenhain's zymogen is also carried to the splenic vein is probable. I have shown that it was through the effects of this ferment that the liver glycogen was converted into sugar, and that the importance of the latter, when distributed to the muscles and other structures in which it is consumed, was very great. That the conversion of glycogen into sugar is a continuous process and that it is independent of digestion are recognized facts,—and necessarily so, since the activity of the functions that entail the use of glycogen may at any moment be increased, the tissues requiring replenishment to a correspondingly great degree at the expense of the liver reserve. How could this predominating function be carried on in the perfect manner that it is, were it connected with, or did it depend upon, any digestive process? Again, if present views prevailed and the amylolytic ferment were to only reach the liver after being secreted in the duodenum by the pancreas, then absorbed by the venules of the villi, how could we account for the conversion of glycogen between the periods of active digestion? That the intestinal tract is not the channel traversed by the portion of pancreatic amylopsin devolved to the conversion of glycogen into sugar is also suggested by familiar experiments.

We have seen that the insertion of a piece of pancreas into the tissues of an animal showing marked glycosuria, after removal of the pancreas, will cause it to disappear. This apparently constitutes a direct contradiction of all the foregoing statements; but such is not the case in reality. Minkowski[43] confirmed the fact, observed by other investigators, that glycogen quickly disappears after removal of the pancreas. This indicates two important features: *i.e.*, that glycogen is no longer formed after removal of the pancreas, and that some other agency converts it into sugar. Why removal of the pancreas should prevent the formation of glycogen may probably be accounted for by the fact that the absence of trypsin causes

[43] Minkowski: Berliner klin. Wochenschrift, No. 5, 1892.

the digestion of albumins in the duodenum to cease, as shown in the Schiff-Herzen experiments. That the conversion of food-starches into maltose is also, owing to the absence of amylopsin, arrested, is evident. The only substitute for this ferment available is ptyalin; but though the salivary secretion —at least, its ptyalin—is quantitatively increased after removal of the pancreas, it is inadequate to convert all the starch required to compensate for the glycogen used. The glycogen, gradually converted by what ptyalin is swallowed with the saliva between meals, therefore disappears. The fact that ptyalin converts starch partly into dextrose greatly hastens the disappearance of the glycogen, the primary sugar of which is mainly maltose. It would seem, therefore, *that the glycosuria following extirpation of the pancreas is due to the action of ptyalin upon food-starches.*

That the salivary secretion is gradually increased after removal of the pancreas is sustained by experimental evidence. Aldehoff[44] observed that glycosuria only appeared from 24 to 48 hours after the operation in turtles; in frogs it only appeared after four or five days, "slight at first, becoming more intense later on." Minkowski[45] found that it sets in after two or three days in dogs, under the same conditions. Again, during its passage through the stomach ptyalin acquires increased energy as a ferment. Charles[46] refers to this question as follows: "Chittenden and Griswold find that the presence of acid, as hydrochloric acid, to the amount of 0.005 per cent. decidedly increases the diastatic action, while an increase beyond this diminishes it, the action stopping with solutions of acid from 0.1 to 0.4 per cent.; the diastatic action of the saliva would, therefore, appear soon to cease in the stomach, but *the peptones* in that organ exercise a decided influence on salivary digestion, stimulating the ferment to *increased action*, particularly in presence of acid, which by itself may completely prevent the conversion of starch into sugar." Mering found that starch acted on by saliva yielded dextrin and maltose at first, then after some time grape-sugar.

[44] Aldehoff: Zeitschrift für Biologie, Munich, Bd. xxviii, p. 293, 1892.
[45] Minkowski: *Loc. cit.*
[46] Charles: *Loc. cit.*

Yet, glycosuria so produced may, we have seen, be prevented by grafting a fragment of pancreas under the skin. Minkowski[47] grafted such fragments in the dog, cat, and pig, removed from the pancreas of these animals. When the graft had become adherent and functionally active, he removed the rest of the pancreas. No glycosuria appeared until the grafted portion itself had been removed. Besides indicating that ptyalin glycosuria prevails after resection of the pancreas, the fact that grafts can preserve normal functions clearly shows that the intestinal canal is not the only region wherein splitting of carbohydrates and proteids may occur. Each graft evidently received its blood through newly-formed vessels. This blood doubtless contained splenic ferment, since, as previously stated, the greater portion of this ferment really enters the general circulation *via* the liver, and ultimately reaches the portal circulation, probably by the hepatic artery, in the experimental animals. Such being the case, it is evident that *the splenic vein can, besides the intestinal villi, serve as a channel for the transmission of the pancreatic and splenic ferments to the liver.*

Here, again, however, we are brought to realize that the splenic ferment is not merely a local agency, but one which during spleno-pancreatic activity forms part of the entire blood-stream. I have given striking evidence of this in Herzen's experiment with blood taken from various arteries and veins. We saw that blood taken from the femoral vessels (arterial and venous) of a dog in full splenic digestion proved active in digesting albumin, and that the blood of the splenic vein was exceedingly active. Indeed, the blood which is so active in the pancreas originates from the cœliac axis, lungs, heart, etc.,—*i.e.*, from the general circulation,—and only contains the proportion of splenic ferment which the entire blood-stream contains. But a question suggests itself here: If, by the combination of trypsinogen and the splenic ferment, trypsin is formed, is it not trypsin-laden blood that re-enters the pancreas? Trypsin *would* re-enter this organ were the relative proportions of the two bodies not regulated by the vagus. As

[47] Minkowski: *Loc. cit.*

we find that a slight excess of splenic ferment will serve the physiological process in the pancreas,—to supply the intestinal canal,—if we grant the vagus even one-tenth of the truly wonderful prerogatives it seems to possess, we can readily assume that, by regulating the quantities of either ferment allowed to enter the blood-stream, it provides just the excess of splenic ferment in the pancreas to insure perfect function during the digestive process: all features which indicate that *trypsin is a constituent of the entire blood-stream when albuminoids are undergoing digestion in the alimentary channels.*

The far-reaching meaning of all this is suggested in the following deductions:—

1. The cleavage processes to which trypsin submits albumins in the intestinal canal include the preliminary steps of a protective function.

2. The spleno-pancreatic internal secretion is represented by the trypsin which reaches the portal vein by way of the splenic vein, and which continues in the blood-stream the cleavage processes begun in the intestinal canal.

3. The main function of the spleno-pancreatic secretion, trypsin, in the blood-stream is to protect the organism from the effects of the toxic derivatives of albuminoid bodies of endogenous or exogenous origin, including toxins.

Since the first and third conclusions were submitted by myself in the first edition of the present work (1903), they have received independent confirmation in many particulars through the researches (begun in 1905) of Abderhalden,[48] who concluded that "each separate cell, with very few exceptions, disposes of the same or similar ferments as those secreted by the digestive glands in the intestinal canal." He termed "defensive ferments," moreover, agents of this class which have for their purpose "to bring the so-called reactions of immunity into close line with processes that are normal and consequently familiar to the cells."

[48] Abderhalden: "Defensive Ferments," third edition, 1914.

CHAPTER IX.

THE ADRENAL SYSTEM IN THE FUNCTIONS OF THE HEART AND LUNGS.

Reference has repeatedly been made to the functional connection between the secretion of the adrenals and the heart. Is this connection direct or is it indirect? In other words, is it the result of a direct stimulation of the heart-muscle such as is produced by suprarenal extract, or of the stimulating effect to which the increase of oxidizing processes, including those of the cardiac cerebro-spinal centers, give rise? Analysis of this question tends to show that both processes prevail simultaneously when from any cause the adrenals become overactive.

THE ADRENAL SECRETION AS THE SOURCE OF THE FUNCTIONAL ACTIVITY OF THE RIGHT HEART.

As freshly-oxidized blood is constantly being supplied to *both* sides of the heart, the specific action of digitalis upon the right heart to which I have referred cannot be ascribed to the oxidizing substance. Again, it would seem that the suprarenal secretion itself could hardly be credited with a local stimulating action upon the cardiac walls when the thickness of the myocardium is recalled, unless the latter be provided with channels calculated to insure the penetration of the secretion to its deeper tissues. Not only do such channels exist, however, but they are so disposed as to enable the adrenal active principle to permeate the entire myocardium and be equally distributed among the contractile elements. The channels to which I ascribe such important functions have been known as the "foramina of Thebesius."

These canals are described in Gray's "Anatomy" as follows: "The foramina Thebesii are numerous minute apertures, the mouths of small veins (venæ cardis minimæ), which *open* on various parts of the inner surface of the auricle. They *return* the blood directly from the muscular substance of the