CHAPTER VIII.

THE INTERNAL SECRETIONS OF THE PANCREAS AND SPLEEN.

GLYCOSURIA AND OVERACTIVITY OF THE ADRENAL SYSTEM.—The pancreas and spleen are considered together because there is considerable evidence in favor of the view that they are functionally associated; and it is to give the analysis of this question and its relationship with the ferments furnished by the pancreas to the portal blood due prominence that we have, under other headings, considered the better-known functions of both organs.

To sustain our belief that liver glycogen is converted into dextrose by an amylolytic ferment supplied by the pancreas which penetrates the portal vein directly,—*i.e.*, by way of the splenic vein,—we were fortunate in having at our disposal the experiments of Croftan, which showed that suprarenal overactivity could so augment the functional activity of the ferment-producing organ as to induce a very great increase in the sugar eliminated. This feature requires further study, since it will tend to elucidate other functions of the pancreas.

We believe that we have conclusively shown that certain drugs and poisons increase the functional activity of the adrenals. The uniformity of the phenomena traceable to these glands under the influence of such agents seems to us to warrant the conclusion that, if we can demonstrate that glycosuria is also subject to the latter, its fluctuations following those of the suprarenal activity or insufficiency induced by them, a direct connection between glycosuria and suprarenal overactivity will have been shown. Yet we must bear in mind, in this connection, that all active drugs *may* have a primary action upon tissues for which they possess a specific affinity before the suprarenal protective functions are fully awakened. We have seen that even electrical stimulation of the splanchnic is only followed by vermicular motions of the intestinal wall after some time elapsed. But too much weight must

not be given this feature, inasmuch as I have personally seen the typical symptoms of total suprarenal insufficiency occur in a dog within twenty seconds after a fatal dose of hydrocyanide of potassium had been administered. Large quantities of the less active drugs are more likely to reach the tissues for which they possess a special predilection, bromide of potassium, for instance, than such an agent as that previously mentioned. While, therefore, we cannot say that excessive formation of sugar, when drugs are given, is due only to overstimulation of the adrenals, we can say that all drugs can produce it when they stimulate suprarenal activity. Furthermore, it seems probable that some drugs not only do this, but they likewise, owing to their affinity for certain tissues, enhance the production of sugar by increasing the functional activity of the intimate structures of the organs concerned in its production from ingested substances—thus stimulating two different sets of organs simultaneously. Such an agent we probably have in phloridzin.

In an able and exhaustive review of the subject of toxic glycosuria, F. Cartier,[1] of Paris, says: "The symptomatology of phloridzin is very limited, seeing that it does not give rise to a true intoxication. . . . In man it is even possible to bring on glycosuria, and maintain it a long time, without giving rise to general disorders, provided a copious alimentation is insured." We have evidence in the last sentence that the main general result is an *excessive formation* of sugar, and, more carbohydrates being required, it is to an excessive production of the converting agent that we must ascribe this phenomenon. Still, if general symptoms are absent, what becomes of the suprarenal overactivity? Cartier answers this question when he says: "Yet *all* authors who have studied phloridzin unite in saying that the animal experimented upon becomes *voracious*, and, if not overfed, rapidly wastes. . . . When alimentation is insufficient, grave phenomena appear. Phloridzinic glycosuria has been obtained in animals entirely deprived of hydrocarbons; under these circumstances general symptoms *analogous to those of diabetic coma* have been observed."

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[1] F. Cartier: Thèse de Paris, 1891.

Osler[2] states that Frerichs recognized three groups of cases; two of these are of special interest to us: *(a)* Those in which after exertion the patients were suddenly attacked with weakness, syncope, somnolence, and gradually deepening unconsciousness, death occurring in a few hours. *(b)* Cases with preliminary gastric disturbance, such as nausea and vomiting, or some local affection, as pharyngitis, phlegmon, or a pulmonary complication. In such cases the attack begins with *headache,* delirium, great distress, and *dyspnœa,* affecting both inspiration and expiration: a condition called by Kussmaul *air-hunger. Cyanosis* may or may not be present. If it is, the *pulse* becomes *rapid and weak* and the patient gradually sinks into *coma,* the attack lasting from one to five days. The need of a copious supply of carbohydrates obviously points to increased oxidation. Indeed, complete absence of glycogen in the liver and muscles has been noted. The voracious appetite and rapid wasting further sustain this —and simultaneously, therefore, the presence of suprarenal overactivity. The italicized words in the list of terminal symptoms, on the other hand, as prominently point to the gradually deepening suprarenal exhaustion.

Alluding to the effects of acids in the production of glycosuria, Cartier refers to the experiments of Pavy[3] with phosphoric acid. An increase of sugar was noted in twenty minutes; fifteen minutes later a large quantity was present. In another strong, but *fasting,* dog the sugar was markedly reduced by a smaller dose. Hæmorrhagic infiltration of the gastric and intestinal tissues and hæmaturia were also noted. These are all familiar landmarks of suprarenal origin. Striking, in this connection, are the observations of Stadelmann,[4] who found that the production of CO_2 decreased in the rabbit during acid intoxications as it does in diabetic coma. In a foot-note Cartier says: "Voit and Pettenkofer and Gaethgens have peremptorily shown, by means of most precise experiments, that (1) the oxygen absorbed by a diabetic is much less than by a normal man, and that it decreases progressively until

[2] Osler: "Practice of Medicine," third edition.
[3] Pavy: Guy's Hospital Reports, vol. of 1861.
[4] Stadelmann: Deutsche med. Wochenschrift, Nov. 4, 1890.

the end of the disease, when it is hardly equal to half of the normal quantity; (2) that the CO_2 exhaled is likewise reduced." That this is essentially due to suprarenal insufficiency—*i.e.,* reduced oxidation—is shown by the fact that, in a case of coma due to meningitis witnessed by Stadelmann, the proportion of CO_2 was 28.2 per cent.; while in diabetic coma the gradual decline is that observed in Minkowski's rabbits, which, from the normal 25 per cent., steadily dropped to 16, 8.8, then 2.9 per cent.

We have seen that tetanus was partly due to adrenal overactivity. Cartier refers to the experiments of Claude Bernard, which showed that strychnine produced glycosuria in dogs. "It is unnecessary to reproduce here," says Cartier, "the symptoms of poisoning produced by this alkaloid; we will simply say that nothing recalls tetanus to such a high degree as does intoxication by it." We have another proof that it is due to an excessive production of a ferment or some other agency possessed of converting powers since Langendorff found that "glycosuria only occurs in frogs when the liver contains glycogen. . . . In the summer, when their liver contains none, strychnine does not cause diabetes in these animals."

We are reminded of the disorganization of hæmoglobin produced by advanced suprarenal insufficiency when, referring to curare glycosuria, Cartier says: "Others account for this glycosuria by an insufficiency of the respiration and by slowing of combustions. The dark coloration of curarized blood indicates this asphyxia." Even the nervous distribution, *as I interpret it,* including the basospinal connection between the pituitary body and the adrenals, finds itself sustained in a remarkable manner by the following lines of Cartier's in reference to morphine glycosuria: "An extremely interesting fact that all these investigations indicate is that one can produce with a toxic substance exactly similar phenomena to those recorded by Claude Bernard in his lessons at the College of France, and obtained by puncture of the medulla, and that these toxic glycosurias can in most cases be arrested, as are glycosurias of nervous origin, by severing the centrifugal nerve-impulse conductors. Indeed, section of the pneumogastric (centripetal nerve) does not prevent glycosuria caused either by Bernard's puncture or by morphine; but, on the contrary,

section of the splanchnic nerves (centrifugal nerves) and of the medulla above the origin of these nerves prevents both the experimental diabetes of Claude Bernard and the toxic diabetes caused by morphine."

The list of drugs that are able to produce glycosuria could be indefinitely prolonged: it includes all those that produce suprarenal overactivity. But this does not mean that the ferment-producing organ is alone stimulated; glycosuria is but one of the manifestations of the exaggerated *general* metabolism induced, and oxidation processes are enhanced accordingly. Toxic glycosuria, therefore, only represents the surplus of sugar which oxidation processes have not consumed; the excess of sugar actually produced is probably far greater than the surplus which the urine shows. Again, certain drugs —phosphorus, for instance—do not produce glycosuria to any marked degree; as soon as the dose capable of causing it is reached, the adrenals lapse into insufficiency, and, if the dose is pushed to any extent, even the normal ratio is reduced. Antipyrin is now considerably employed in diabetes; we have seen that this drug and acetanilid readily produced suprarenal insufficiency and dissociation of the hæmoglobin molecule. This is sufficiently extensive sometimes to manifest itself as methæmoglobinuria or even hæmatoporphyrinuria. All these facts seem to me to indicate that *toxic glycosuria is primarily due to overstimulation of the adrenal system, the excessive functional activity which increased oxidation produces giving rise to an inordinate production of an agency that converts glycogen into sugar*. All these features will again be reviewed.

That the agency which converts glycogen into sugar is the amylolytic ferment produced by the pancreas to which I have referred is further sustained by the foregoing facts, especially in view of the amylolytic properties of the pancreatic secretion in the intestine. Since the conversion into sugar occurs during fasting as well as during digestion under the effects of toxics, the reaction can only include the hepatic glycogen and pancreatic ferment; and, there being nothing in the intestine to convert during fasting, the ferment must necessarily reach the glycogen by another channel. *May this not be the more direct route afforded by the splenic vein?*

Yet there is a possibility that the flow of amylopsin in the intestine, which the enhanced activity of the pancreas must undoubtedly increase, may be reabsorbed by the venules, and, being carried into the portal system, produce conversion of the glycogen precisely as if it had entered the portal vein by the way of the splenic vein. But we have seen that, while removal of the pancreas is rapidly followed by death, very large portions of the gland can be safely removed. Admitting that the operators may have left the portions related with the pancreatic duct, how could we account for the effects of transplanted fragments in arresting the glycosuria caused by removal of the pancreas, recorded by Minkowski[5] and Hédon?[6] As long as fragments transplanted subcutaneously remained normal no glycosuria occurred; it reappeared, however, when these fragments became histologically impaired. It is evident that the only channel here for the amylolytic ferment produced could be the blood. Thus carried to the heart, it then penetrated the liver by way of the hepatic artery, and reached the intercellular capillaries and the glycogen precisely as if it had penetrated the organ by way of the portal vein. Although but a small quantity of the ferment could thus reach the liver, it was evidently sufficient to convert the amount of glycogen required to build up the very limited proportion of sugar found in the normal blood, as previously shown. Again, we have seen that the product of intestinal reduction is maltose, while the urine of Croftan's animals when stimulated with suprarenal extract gave dextrose in very great quantities: a feature denoting successive processes. This and the other facts adduced appear to me to contribute additional evidence to my view that *the dextrose-forming ferment enters the portal system by way of the splenic vein.*

THE FUNCTIONAL RELATIONSHIP BETWEEN THE PANCREAS AND SPLEEN.

The internal secretion of the pancreas and that of the spleen may perhaps be best studied by submitting to a careful analysis the hypothesis advanced by Schiff, sustained by

[5] Minkowski: Verhandl. d. XI Congr. für Inn. Medicin, Wiesbaden, 1892.
[6] Hédon: Archives de Physiologie norm. et path., vol. iv, 1900.

Herzen,[7] and defended by Lépine[8] and others that the spleen supplies a ferment which, when added to pancreatic juice, greatly increases its digestive energy. Schiff believed that the splenic substance played an important part in the genesis of the pancreatic proteolytic ferment, but Herzen attributed to it the function of converting trypsinogen into trypsin, the albumin-solving constituent of the pancreatic juice. This subject was more recently studied experimentally by Gachet and Pachon,[9] who were led to conclude, as previously suggested by Laguesse (1893) and Schäfer (1895), that the spleen furnishes a true internal secretion which possesses a special affinity for the pancreas, the protrypsin of which it transforms into trypsin, as suggested by Herzen. This substance loses its properties at the boiling-point; is precipitated, when in aqueous solution, by alcohol; and is, therefore, of the nature of a ferment.

Lépine also confirmed Schiff's and Herzen's view by experiments *in vitro* and by blood-analyses. He found that a mixture of pancreas and spleen-pulp in glycerin possessed far more active properties than pancreas alone similarly prepared. On the other hand, the blood of an animal deprived of its spleen proved almost inert as a tryptic, while the blood of a normal dog possessed distinct digestive powers. Analysis of the experiments of these various authors distinctly indicates that some function of the kind mentioned exists. The anatomical relations of the organs involved, however, make it impossible for the internal secretion referred to to penetrate the circulation without first passing through the liver *with the blood of the splenic vein, which collects the pancreatic internal secretion and carries it to the portal vein.* This fact seems to suggest that, besides the amylolytic ferment, the portal carries a ferment to the liver calculated to insure the tryptic action upon albumins and kindred bodies. If we consider that we have in the blood of the portal channels all the products of digestion and that trypsin is "applied solely to albuminoid

[7] Herzen: Revue Générale des Sciences pures et appl., vol., 1895.
[8] Lépine: Société des Sciences Médicales de Lyon, July, 1895.
[9] Gachet and Pachon: Archives de Physiologie, April, 1898.

conversions and changes" (Charles), the importance of the spleen's internal secretion will appear.

Albuminoids, especially those ingested with food, are not the inoffensive bodies that they appear to be; indeed, they constitute the foundation of some of the most dangerous substances that enter the organism when their molecular structure undergoes certain changes. Apart from any function of the spleen in the direction mentioned, the pancreatic trypsin supplied to the intestine—if we can judge by the manner in which a small remnant of pancreas will prevent glycosuria—must persist even when the pancreas is in a state of advanced disease. We saw that one-eleventh of the functional area of the adrenals sufficed to sustain the general oxidation processes. That the pancreas possesses at least four times more functional area than it absolutely needs has been experimentally demonstrated. With proper—fresh, uncontaminated—food, a normal organism is practically invulnerable, so splendidly is it armed against any chemico-physical decomposition that the ingesta may undergo. But these physiological defenses may be weakened through general or local adynamia, *i.e.,* lowered oxidation processes, and peptones, capable of yielding *toxalbumins, leucomaines, ptomaines,—all* albuminoids,—fail to undergo further splitting in the intestinal canal. Again, and under the same circumstances, notwithstanding the destructive action of the gastric and intestinal secretions, bacteria and their toxins may penetrate the debilitated villi and the portal circulation. The blood-stream, furthermore, may be invaded through peripheral organs not only by bacteria and their *toxins,* but also by *vegetable poisons* and venoms: *all* albuminoid substances, as previously emphasized. Even these do not represent all the sources of danger that a protective function, such as that represented by the pancreatic and splenic secretions, would have to meet, were they, as I believe, mainly intended to fulfill such a mission.

If toxic albuminoids reach the portal vein by way of the intestinal villi and the mesenteric veins, all conditions therein are most advantageous for the action which trypsin is known to exercise upon them: It acts with great energy in alkaline media, and the presence of oxygen does not inhibit its action;

if, therefore, the venous blood of the afferent channels should happen to contain an unusual amount of oxidizing substance through suprarenal overactivity, the tryptic disruption of peptones would not, to say the least, be prevented; in laboratory experiments the need of an antiseptic when pancreatic juice is used is well known; we have seen that, in the afferent vessels, the fluids derived from the intestines had been saturated therein with the antiseptic secretion of the glands of Brunner and Lieberkühn, and it is evident that their influence would normally continue in the venous channels; finally, the action of trypsin does not cease when the peptone stage is reached; it converts these into leucin, tyrosin, aspartic acid, etc., the fate of which derivatives I have traced down to urea, the end-product eliminated in the urine.

The rôle played by the spleen in the pancreatic digestion of proteids, and to which I add a prophylactic function, has been so ably reviewed by H. F. Bellamy in a comparatively recent number of the London *Lancet*[10] that I will utilize the greater part of his paper to illustrate the various features that appear to me to furnish a solid foundation, not only for the views of Schiff and Herzen, but also for my own.

The author reviews the history of the question as follows: "Corvisart found that in dogs in full digestion there was for a certain time a constant rise to maximum in the digestive power of the pancreatic juice, succeeded by an equally constant fall to minimum. The maximum was attained during the eighth hour after the ingestion of a meal; the minimum from the thirteenth to the eighteenth hours. Meissner announced that in fasting animals the pancreatic juice possessed little or no peptonizing power. Schiff, after a number of experiments on such animals as rats, guinea-pigs, rabbits, and young dogs or dogs of small breed, found that during fast the pancreas really possessed almost no peptonizing power; the albumin imprisoned in the duodenum remained there for whole hours without dissolving, the infusion of the gland giving results equally negative. On the other hand, in the case of ravens and adult dogs of large breed the pancreas preserved during fast a certain digestive power, even in animals in a condition

[10] H. F. Bellamy: London Lancet, Oct. 27, 1900.

of complete fast which had digested a copious meal the day before; under these circumstances, indeed, the infusion of the whole pancreas of a large dog was capable of digesting from 50 to 60 grammes of albumin. In such dogs this condition of weak digestion was maintained until toward the fourth hour after the meal, after which time digestion proceeded very much more rapidly, so that at the time of maximum the pancreatic infusion was capable of digesting from 50 to 60 grammes of albumin. As regard cats and small dogs, he was able to confirm the results of Corvisart. By these experiments, then, the above-mentioned observers succeeded in establishing the following two facts: (1) that the activity of the pancreatic juice or of an infusion of the gland is not continuous, but intermittent, and (2) that maximal activity appears regularly during the culmen of gastric digestion (from six to eight hours after a meal), at which time it is very considerable."

Passing now, for the moment, from the pancreas to the spleen, he proceeds briefly to examine the behavior of this organ in relation to digestive phases. "Lauret and Lassaigne in 1825 discovered that the spleen began to become congested at the moment when the stomach discharged chyle abundantly into the duodenum; that this is, however, merely a coincidence is shown by the fact that the congestion also occurs after ligature of the pylorus. Dobson in 1847 discovered that in a dog three hours after a meal the spleen is still as small and as anæmic as during fast; that it commences to dilate in the fourth hour after a meal; that five hours after it has attained its maximal turgescence, decreasing afterward from the seventh hour to attain toward the twelfth its minimal volume. Landois in the same year found that in the rabbit the relative weight of the spleen to the body-weight of the animal was the same two hours after a meal as after forty-eight hours of fast; that it increased considerably from the fifth hour, remaining high until the twelfth hour. . . . . .

"The striking synchronism in the splenic congestion and the presence of trypsin in large quantity in the pancreatic juice or in an infusion of the gland was observed by Schiff and caused him to repeat all his former experiments on the tryptic digestion of albumins, this time on animals in which the spleen

had been for some time removed and on others in which it was prevented from dilating by ligature of its hilum at the time of the experiment. He experimented in this way upon a very large number of dogs and cats; nearly all his experiments were double: *i.e.*, performed at the same time and in the same manner on two animals selected so as to resemble one another as much as possible, and in only one of which had the spleen been extirpated or ligatured. These experiments were of two kinds: (1) those conducted with pancreatic infusions, and (2) those carried out in the living duodenum, the following being typical examples:—

"*I. Infusions. Ligature of the Hilum of the Spleen.*—Two cats, after fasting for 19 hours, received as much meat as they would eat; 1 hour afterward they were etherized, and the spleens, which were found to be in a state of contraction, were brought out through a wound in the abdomen and their hila were encircled by strong thread; in one of the animals the hilum was firmly tied, but in the other it was simply encircled and a knot was tied, leaving the splenic circulation perfectly free (this was done in the endeavor to equalize traumatic conditions as much as possible). The spleens were then replaced in the abdominal cavity and the wound was sutured. On recovering from the anæsthesia the animals did not appear to suffer. They were killed 6 hours later. Gastric digestion was found to be more advanced in the animal in which the splenic vessels were tied; the pancreas of both was cut up into small fragments and infused with 100 cubic centimeters of water for an hour at 35° C.; the liquid was afterward decanted and returned to the warm chamber together with cubes of albumin.

"*Result.*—In 7 hours the pancreatic infusion of the cat in which the hilum was not ligatured digested 17 grammes of albumin; that of the other did not digest at all even at the end of 12 hours.

"This experiment was performed on a large number of cats and dogs and always gave the same result. In spite, however, of the perfection of gastric digestion in the operated animals, it was possible to lay at the door of traumatism the absence of duodenal digestion; to correct this the experiment was repeated as follows:—

"*Extirpation of the Spleen.*—Two dogs—one normal, the other having undergone splenectomy a month previously, but at the time of the experiment in perfect health—were operated upon, while fasting, as follows: Etherization, ligature of the pylorus, injection into the stomach, per œsophagus laid bare and opened, of 50 grammes of peptone and 2 grammes of dextrin; to allow drainage of swallowed saliva the œsophagus was ligatured below the opening. Both animals were killed five hours later, and each pancreas was infused for three-fourths of an hour in 100 cubic centimeters of water at 35° C. Although death had occurred before the most favorable moment for the experiment,—*i.e.*, in advance of the summit of the splenic curve,—the infusion coming from the dog with the spleen intact digested 17 grammes of albumin in 17 hours, while the other digested nothing even in 18 hours. Numerous experiments made in this manner always gave the same result. The spleenless dogs had in many cases undergone splenectomy several months before the experiment, and the determination in them of perfect conditions of health was always a matter of great care.

"*II. Experiments in the Living Duodenum. Ligature of the Duodenum at Both Ends.*—Two dogs after fasting for 17 hours received as much meat as they would eat and immediately afterward were operated upon as follows: Etherization, laparotomy, ligature of the pylorus and of the bile-duct, introduction into the duodenum of from 30 to 40 grammes of albumin, and ligature of the jejunal end. In one of the animals the splenic hilum was also ligatured. Both were killed 7 hours later.

"*Result.*—In the dog with the splenic hilum tied the albumin was found to be intact; it had, however, disappeared in the other.

"This experiment was also several times repeated on animals which had undergone splenectomy a long time previously, and always yielded the same result; it is, of course, capable of being combined with the preceding by making an infusion of the pancreas after the death of the animals. Such infusions give results in harmony with those furnished by the duodenum itself. Further, it will be remembered that in the pancreatic