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

heart. Some of these foramina are minute depressions in the walls of the heart, presenting a closed extremity."[1] This information would afford but little light could we not supplement it with an excellent paper by F. H. Pratt,[2] in which the *nutrition* of the heart through the vessels of Thebesius and the coronary veins is studied. How much we are indebted to the author for his investigations is suggested by the following remarks: "So far as I have been able to determine, no *experimental* physiological work has ever before been done on the vessels of Thebesius; all opinion regarding their functional importance has rested upon the assumption that they only serve as veins, conveying a part of the venous blood from the coronary capillaries through the foramina Thebesii into the cavities of the heart."

After referring to the labors of Thebesius (1708), Vieussens (1757), Haller (1786), and Abernethy (1798), the author reviews the more modern investigations of Bochdalek,[3] which led to the conclusion "that the greater number of the small openings on the inner surface of the right as well as the left auricle, which from early times have borne the name of foramina Thebesii, represent the mouths of little veins that, *often uniting into larger vessels,* course with many branches *through the auricular walls.*" Langer's researches[4] on the foramina of the human heart are next analyzed. "With the aid of the blow-pipe, and by means of a watery injection-mass colored with Berlin blue, he demonstrated these foramina *in all the cavities* of the heart. He succeeded in injecting the vessels of Thebesius not only from the coronary vessels, but from the *endocardial* surfaces as well. Bochdalek's observations regarding the presence in both auricles of foramina Thebesii were thus confirmed, and the fact of a communication between the coronary vessels and each of the four cavities of the heart was thoroughly established. The foramina which Langer found on the endocardial surfaces of both ventricles were similar to those in the auricles, but much smaller. They

[1] All italics are our own.
[2] F. H. Pratt: American Journal of Physiology, vol. i, p. 86, 1898.
[3] Bochdalek: Archiv für Anat. u. Phys. u. wiss. Med., Leipzig, p. 314, 1868.
[4] Langer: Sitzb. der k. Akad. der Wissensch. zu Wien, 1880, Bd. lxxxii, 3 Abth., p. 25.

were most conspicuous on the papillary muscles and in the *neighborhood of the great vessels,* being less easily seen in the region of the apex, where they were obscured by the trabecular net-work."

Very suggestive in connection with my own views are also the observations of Gad[5] on the vessels of Thebesius in the ox, and to which Pratt refers in the following words: "In the method which he describes for demonstrating the action of the valves of the *left* heart, wherein water under pressure is made to fill the ventricle and aorta, he noticed that water flowed into the *right* heart from the foramina Thebesii. On illuminating the interior of the left ventricle he was enabled to see fine, blood-stained streams issuing from the endocardial wall into the clear water with which the cavity was filled." Finally he reviews the labors of Magrath and Kennedy,[6] who, "working with artificial circulations of defibrinated blood on the isolated heart of the cat, observed that a small portion of the *coronary blood* found its way into the *left ventricle.* The only possible source of access other than from the vessels of Thebesius was leakage past the aortic valves. This leakage, as shown by a manometer-record of aortic pressure, did not occur." The author closes his review of the literature of the subject with the statement that "notwithstanding these painstaking observations, the vessels of Thebesius still occupy a very obscure position in anatomical literature. Foramina Thebesii are referred to as constant in the right auricle, forming in part the mouths of small veins. Their occurrence in the left auricle is occasionally mentioned. But the fact that *the vessels of Thebesius open into all the chambers of the heart*—ventricles as well as auricles—is hardly recognized."[7]

In the author's own experiments, various agents were injected at a constant pressure, through the coronaries of fresh, often still living, hearts of the rabbit and dog. They showed that liquids in these vessels penetrate into the heart cavities through the endocardial foramina, thus verifying the foregoing

[5] Gad: Archiv für Physiologie, p. 380, 1886.
[6] Magrath and Kennedy: Journal of Experimental Medicine, vol. ii, p. 13, 1897.
[7] All italics are our own.

data. As the cannula was tied directly into the artery, the liquid could only reach the cavities through the foramina, while in all experiments care was taken to avoid high pressures. In the heart of the ox the endocardial depressions were found "regularly *larger in the auricles* than in the ventricles," while in the right auricle "they may," he states, "be provided with thin, single valves, *especially about the origin of the great veins.*" In the left auricle the depressions are fewer in number and unprovided with valves. "Foramina Thebesii are *never absent from the ventricles,*" says Dr. Pratt. "In the *right* ventricle, which is *especially well provided with them,* the larger number are seen upon the septal wall. It is often *much more difficult to find them in the left ventricle,* although a diligent search is never without a reward" . . . "structures, accessory to these ventricular foramina, which might in any way serve the office of valves I have not seen." . . . "On the injection of the vessels of Thebesius with air by means of the blow-pipe applied to the foramina, characteristic, fine, *subendocardial ramifications,* which very frequently conduct the air into other Thebesian systems, or *even into the great coronary veins* will seldom fail to appear." The latter point is also sustained by experimental evidence.

The fact that the right side of the heart is endowed with a more perfect system of canalization than the left is suggested by the following remarks: "The ease with which injections of air and blood could be made to demonstrate the connection between the vessels of Thebesius and the coronary veins caused me to doubt the opinion expressed by Langer that the foramina Thebesii in the ventricles *communicate with the veins by capillaries alone.* To settle this point, I injected the coronary veins of the ox with starch and celloidin masses, both too thick to pass the capillaries, and found that even these emerged from the foramina Thebesii of the right ventricle. So intimate a connection, however, between the coronary veins and the vessels entering the *left ventricle I have not yet been able to demonstrate.*" The author also says: "By means of a very successful corrosion preparation, made by injecting the veins of an ox-heart with celloidin, I was able to trace the communication. In this preparation the position of some of the foramina

Thebesii was marked by small disks of the hardened mass formed by the oozing out of the celloidin upon the endocardium. These foramina were shown to be connected with the smaller *coronary veins* by fine branches. The still finer ramifications which, as Langer has demonstrated, lead from the foramina and branch directly into capillaries were here uninjected; they would appear only when injected from the foramina themselves."

The only connection between the vessels of Thebesius and the coronary arteries that he could find, notwithstanding repeated attempts, was by capillaries. Bochdalek having observed that the foramina of one auricle communicated with those of the other, he was able by blow-pipe injection to verify the correctness of this view, the air of one auricle having passed out through a similar exit into the other.

To sustain his view that the nutrition of the heart may be carried through the vessels of Thebesius some time after the coronary arteries are absolutely obliterated, a number of experiments are related. Thus, fluid introduced into the ventricle of an isolated heart, by means of a cannula passed down to this cavity, and tightly held *in situ* by a ligature passed around the auriculo-ventricular groove, only found its way through the vessels of Thebesius. Defibrinated blood, inserted into the organ through this cannula, brought on, often within one minute, "strongly marked, co-ordinated contraction of the ventricle." As the blood thus introduced would become venous, the action would become gradually reduced, but renewal of the blood would at once cause the heart to resume its normal action. "With a periodic supply of blood," says the author, "and with favorable temperature and moisture this may continue several hours." That mere mechanical stimulation by distension did not cause the phenomena witnessed is demonstrated by the alternate use of Ringer's solution and defibrinated blood. While the solution failed to sustain contractions, blood always succeeded.

Another experiment served to demonstrate that a true circulation could take place between the vessels of Thebesius and the coronary veins. The organ being disposed as stated above, two of the coronary *veins* were incised; "a small, but

steady, stream of venous blood issued from them." Under the same conditions the descending branch of the left coronary *artery* was opened. "No flow of blood occurred from the artery, although there was a free escape from an incision in an accompanying vein." In still another experiment the trunks of both coronary arteries were ligated and the ligature around the ventricles omitted. "The supply-cannula was tied into the ventricle through the oarta. On the introduction of blood the left ventricle alone began to beat strongly and regularly . . . the blood found its way in part into the right ventricle, coming of necessity through the walls. . . ." The blood from the left ventricle had thus found its way into the right one. Finally, he refers to the striking analogy which this nutritional system presents to that of the frog and cat. In the frog the heart is almost entirely nourished "through the branching passages that carry the blood from the interior of the heart nearly to the pericardial surface."

On the strength of all this evidence, Dr. Pratt concludes (giving only the features that bear directly upon the question we are analyzing) that: "1. The vessels of Thebesius open from the ventricles and auricles into a system of fine branches that communicate with the coronary arteries and veins by means of capillaries, and with the veins—but not with the arteries—by passages of somewhat larger size. 2. These vessels are capable of bringing from the ventricular cavities to the heart-muscle sufficient nutriment to maintain long-continued, rhythmic contractions. 3. The heart may also be effectively nourished by means of a flow of blood from the auricle back into the coronary sinus and veins." The author concludes with the very appropriate remark: "It is evident that the nutrition through the vessels of Thebesius and the coronary veins must modify in no slight degree the existing views of the nutrition of the mammalian heart, and of the manner in which infarction of the heart takes place." The clinical features of this question will be considered elsewhere.

Viewed from my standpoint, *the vessels of Thebesius are more concerned with the dynamics of the heart than with the nutrition of this organ,* though the latter function is not to be ignored, particularly in the sense emphasized by Pratt: *i.e.,*

as a source of compensation. That nutrition of the left heart, auricle and ventricle, constantly filled with arterial blood, can result from a flow of the latter through the Thebesian vessels seems clear, but nutrition can hardly be associated with a similar process in the *right* heart, with nothing but *venous* blood to propel through the Thebesian channels. That nutrition, the recognized prerogative of arterial blood, owing to its oxygen, cannot be the active factor here is evident.

The right heart seems, judging from the anatomical arrangement of the parts concerned in the process, to play a physiological function of a special kind. While the Thebesian openings are larger in the auricles than in the ventricles, in the left auricle they are also fewer than in the right; but even more suggestive is the fact that, while some openings in the right auricle are supplied with valves, none have been found in those of the left. Again, both ventricles are supplied with foramina; the right ventricle is particularly well provided with them, while they are difficult to find in the left one. That the septal wall should show them most clearly on the right side is also suggestive. Evidently a similar condition exists between the auricles, as suggested by Bochdalek and confirmed by Pratt; but the fact that limited information supplied by works on anatomy usually covers only those of the right auricle points to greater prominence of the latter. Thus, Gray[8] states that the venæ Thebesii open "on the inner surface of the right auricle." Finally, the openings supplied with valves are in the right auricle, as we have seen; but they are also stated to be most conspicuous in the neighborhood of the great vessels; hence it must only be the Thebesian openings around the great vessels of the right auricle—the venæ cavæ and the pulmonary artery—that are provided with valves.

If we can now ascertain whether the current which enters the Thebesian vessels from the right auricle is shut *out* in this location, or secured *within* the channels, according to the manner in which the valves close,—*i.e.,* inwardly or outwardly,—we will be able to decide whether *venous* blood from the venæ

[8] Gray: "Anatomy;" edition, 1901, p. 622.

cavæ or arterial blood from the lungs circulates in the Thebesian system.

Bochdalek found that many of these openings in the auricles "presented the appearance of blind depressions, since they were often covered with single valves in such a way as to resist investigation with the blow-pipe" . . . "some were slit-like, resembling the mouths of the ureters; still others were large, round depressions, with smaller openings at the bottom." The first remark suggests that the openings serve as exits into the auricle, while the second points to the contrary, since it is difficult to conceive of a *depression* with "openings at the bottom" as a valve calculated to resist liquids exerting pressure on the concave side. From the left auricle Gad caused water to pass out of the right and left ventricular walls, but, as the auricular openings have no valves, this only serves to emphasize the extensive canalization which the Thebesian system represents. The system might, therefore, be considered as essentially calculated to distribute venous blood from the right auricle to the entire heart: a fact which the free anastomosis with the venous channels would seem to sustain.

Pratt states that he has seen "structures accessory to these *ventricular* foramina which might in any way serve the office of valves" . . . "the edge of the foramen is usually sharply defined and may frequently exist as a partial, *shelf-like,* covering, giving the impression perhaps of an attempt at a membranous valve; but it is seldom more than this." A shelf means a projection, and the fact that it is membranous suggests that during ventricular *contraction* this valve is pressed against the opening and closes it: a feature which involves the possibility that during diastole a current—whether venous or arterial—flows into the ventricle through its foramina. That the latter and their valves open inwardly—*i.e.,* in the ventricle—is demonstrated by Pratt's experiment, in which he injected the coronary *veins* with starch and celloidin and found that even these passed *into* the ventricle. If, therefore, the venous blood of the right heart at all enters the muscular *walls* it is not through the foramina of the ventricle, *i.e.,* from below; it must be through the openings above, *i.e.,* those in

the right auricle. The experiment in which the cannula was tied in the pulmonary artery, the blood being "allowed to enter the right auricle through insufficiency of the tricuspid," appears to us to further sustain this fact. The heart continued "its rhythmic contractions for eight hours: a period considerably in excess of that observed in nutrition through the vessels of Thebesius alone. It was inferred that blood had gained access from the auricle to the coronary veins and had thus aided materially in the nutrition." While this course may have been taken by some of the blood in the experiment, it is obviously not a normal one during life, and the unusual duration of the contractions seems to us to indicate that the blood that penetrated into the right auricle found its way into the Thebesian system *via* the openings in this auricle, thus approximating as nearly as possible normal conditions.

The relations between the coronary veins and the Thebesian channels are self-evident, excepting, however, a theoretical back-flow from the auricles into the veins suggested by Pratt, which appears to us abnormal; at least it is not compatible with our views of the process. The Thebesian vessels and coronary veins were found to communicate freely on the right side, but not on the left, with the ventricular foramina. The septal foramina were also found to communicate with the coronary vein at the end of the sinus. An interesting feature is the fact that blood passed into the right ventricle flowed freely from a cut vein of the *left* heart (experiment of April 3, 1897). On the other hand, the relations between the coronary arteries and the Thebesian vessels are of a peculiar kind; thus the communication between the *left* coronary artery and the *right* ventricle seems as free as that between the same artery and the *left* ventricle (through the Thebesian channel) is limited. The experiment in which a colored solution was passed into the left coronary artery caused an accumulation of 400 cubic centimeters to flow from the right ventricle, while only 4 cubic centimeters flowed from the left, sufficiently emphasizes this fact. Haller, who had observed that injected substances flowed out freely from the surfaces of both ventricles, states that "the passage from the arteries into the cavities of the left side is more difficult."

All these features seem fully to supply the needs of the function with which the secretion of the suprarenal glands must be connected, if the phenomena witnessed in many disorders and after the use of most remedies have been correctly interpreted. That we are in the presence of a dual process of which the suprarenal secretion, operating in the right heart, and the arterialized blood in the left heart are active factors seems probable. Again, the marked power of arterial blood —or rather of plasma—since the defibrinated blood filtered through cotton was used—to sustain functional activity, even when only poured into the ventricles, as shown by Pratt, certainly indicates that the blood must alone be able, during life, to compensate, in case of need, for insufficiency of blood furnished by the coronary arteries.

The contractions of the *left heart* seem to me to be greatly assisted by the arterial blood that enters it, and mainly by that which enters the cavities themselves. The experiments of Pratt having shown that contraction could be produced by contact with arterialized blood, the arrival into the *auricle* of a normal quantity of this fluid must be fully capable, therefore, of causing contraction of the walls of that cavity. The relations of the several structures and the mechanism involved are in all probability as follows: The main structures upon which the arterial blood reacts are (1) the musculi pectinati and (2) the sinus venosus and appendix auriculæ, all of which are so disposed as to offer as much surface as possible to the blood. The walls of the cavities mentioned are provided with numerous channels, the Thebesian "veins," to satisfy this purpose. The blood which enters the auricle when it is dilated penetrates all the circuitous areas around the musculi pectinati and into the Thebesian vessels, and the ensuing contraction forces the blood-plasma into the smaller subdivisions of these vessels. from which they find their way into the auricular veins. When the arterial blood reaches the *ventricle,* a process similar to the preceding occurs. The columnæ carneæ are disposed so as to offer considerable surface to the blood, while the ventricular walls are permeated with Thebesian channels, into which the blood penetrates during diastole. The contraction induced closes the apertures of these channels, and forces the blood-

plasma into their smaller ramifications and finally into the veins. The larger channels carry the corpuscular elements to the latter. The rôle of the coronary arteries will be referred to later on.

The *right heart,* as I view the process, owes its functional activity mainly to the suprarenal secretion brought to the cavities by the vena cava. I have sufficiently emphasized the power of this agent to restore cardiac action and sustain it even when the entire spinal cord has been obliterated. The manner in which it exercises its powers is similar to that of the arterial blood on the left side. On penetrating the auricle the contractile structures are submitted to its immediate effects; but the orifices of the Thebesian vessels or channels are more numerous and larger than in the left auricle. The membranous edges previously referred to as valves by the investigators quoted do not appear to me to merit being considered as such after careful examination of these structures in the ox-heart. The aperture being closed by the least squeezing of the tissues containing them, it seems evident that they should as readily close under the powerful contraction of the auricular tissues. The right ventricle also presents a very much larger number of Thebesian orifices than the left, while its walls, though thinner, plainly show the ramifications of these channels. That the venous blood charged with suprarenal secretion should at once penetrate the latter when the ventricle begins to contract is self-evident. Return of the blood to the circulation is effected in the same way as in the case of the left heart: *i.e.,* through the coronary veins.

The whole process is an exceedingly uncomplicated one, but, as we shall see later on, it simplifies many obscure problems, while affording, in connection with the coronary arterial blood, a supply in keeping with the vital importance of the organ itself. Again, Dr. Pratt's experiment, in which blood injected into the *left* auricle flowed freely from the right ventricle, emphasized the possibility of compensation in case of need. Thus, while under normal conditions, the pressure in both ventricles must be equal, reduced contraction—of the right ventricle, for example—through insufficiency of the adrenals would automatically cause the arrival into it, through