juice of dogs of large breed Schiff generally found, even while fasting, a certain quantity of trypsin; when the same were spleenless, however, he was unable to find any.

"Digestion in the Normal Duodenum Provided with a Fistula.—A duodenal fistula was established in a dog. After complete recovery a measured and constant quantity of albumin was introduced every day into the duodenum inclosed in a small envelope of fibrous membrane fixed to the cannula by a thread some centimeters long. The progress of digestion was then observed, the following results being obtained: 1. When the animal was fasting the albumin took from 5 to 6 hours to become dissolved. 2. When the albumin was introduced into the duodenum during the 2 to 3 hours immediately following the ingestion of a meal by the animal it remained unchanged. 3. When introduced 4 hours after a meal it disappeared very quickly,—in about half the time, in fact, occupied during fast. These facts having been duly noted, the spleen was then extirpated, and after complete recovery the same experiment was repeated; very different results were now obtained. Whether fasting or in full digestion the time taken for the digestion of the albumin was exactly the same, viz.: from 5 to 6 hours. The acceleration in the peptonization which had formerly appeared after the fourth hour of digestion, and which coincided both with the appearance of trypsin in the pancreatic juice and with the dilation of the spleen, was now absent. The slow digestion (from 5 to 6 hours) in this experiment was probably entirely due to the secretion of the duodenal glands, which possess only a very feeble digestive power; the active, rapid digestion was due to the appearance, in large quantity, of trypsin in the pancreatic juice: a phenomenon wanting in the spleenless animal. . . . Schiff endeavored to interpret the facts by the following theory: During the congestion of the spleen a substance is produced within it which, carried away by the blood, gives to the pancreas the wherewithal to form its peptonizing ferment. . . . In 1872, however, the theory of Schiff received a rude shock through the great discovery of the zymogens by Heidenhain and his pupils. From the researches of this observer it appeared that, as the gastric mucous membrane forms at the

outset hardly any active pepsin, but a zymogen accumulating in its glands in the intervals of digestion, so the pancreas does not at once elaborate active trypsin but a substance destined to become trypsin under certain conditions and in a certain phase of the digestive act, this substance being, of course, the pancreatic zymogen trypsinogen, or protrypsin. The researches of Heidenhain are well known, and it suffices to recall here only one or more essential points: Thus from them we know that the pancreas of a fasting dog contains little or no trypsin, but merely trypsinogen; consequently its glycerin infusion possesses little or no digestive power; the infusion, however, of a dog in full digestion digests rapidly and copiously, because it contains trypsin. If the pancreas of a fasting dog be divided into two equal portions, one of which is infused at once and the other only after an exposure of 24 hours to the air, the first is found to be inactive, while the other is immediately and energetically active, from which it is clear that the inert trypsinogen which it contains becomes spontaneously transformed into active trypsin; indeed, it suffices to pass a current of oxygen through a pancreatic infusion, rich in trypsinogen and poor in trypsin (an active infusion), to transform it into an infusion possessing a digestive power. This transformation, then, is an oxidation, trypsin being oxidized trypsinogen.

"The fact observed by Heidenhain of the continuous formation and storing up of trypsinogen in the pancreas and its subsequent transformation into trypsin during the culmen of gastric digestion proved that the former substance at any rate enjoyed an origin quite independent of all influence outside the pancreas itself, and the hypothesis of Schiff as to the intervention of the spleen seemed, in consequence, to be at fault. But it was only the theory of Schiff which suffered by these new revelations; as far as the experimental results of the two observers were concerned, physiologists were face to face with two series of apparently contradictory facts—apparently because facts properly observed can never stand in contradiction with one another, and when they appear to do so it is merely because the interpretation of them is either false or incomplete. It fell to the lot of M. Herzen to unravel the tangled hypotheses. It appeared to him that, by modifying the hy-

pothesis of Schiff as to the manner in which the spleen acts as a tryptogene, a fusion of the respective facts of Schiff and Heidenhain could be brought about, and that, far from being antagonistic, they could be shown to be reciprocally corroborative. He argued thus: since the zymogen, even in splenectomized animals, is being continuously elaborated, and therefore independently of the spleen and its periodical congestion, and that it accumulates in the gland-cells during fast, but that it becomes rapidly and copiously transformed into trypsin only in the presence of the spleen and in direct proportion to its dilation, it would seem feasible that the spleen produces, by 'internal secretion' during its congestion, an unknown substance, which, carried away by the circulating blood, transforms the inert zymogen already deposited in the pancreas into active trypsin destined to pass into the secretion of the gland, and that the influence exercised upon the zymogen by this product of the spleen seemed to be a condition *sine qua non* for the transformation of the former into trypsin, at least in the living pancreas, since in the dead organ or its infusion it is so transformed by direct oxidation. This hypothesis of Herzen would seem to be further confirmed by the fact gleaned from the researches of both Schiff and Heidenhain, to wit: that the holding in zymogen of the pancreas at a given moment either of fast or digestion is always in inverse ratio to its holding in trypsin, and *vice versa,* while the latter is always in direct proportion to the spleen dilation.

"So far so good. But Herzen reasoned further. If the spleen really produces, during its congestion, a substance which brings about the transformation of the pancreatic zymogen into trypsin, it would then be possible to seize upon this substance in the spleen itself while in its turgescent condition (from 6 to 7 hours after a meal), and by at once making an infusion of it and mixing a certain quantity of this splenic infusion with pancreatic infusion made from the pancreas of a fasting animal (very rich in zymogen and very poor in trypsin, and consequently nearly inactive) there could be obtained *in vitro* a rapid and copious formation of trypsin easily recognizable by the amount of proteid digested in a given time. The control experiment would also be very simple, consisting merely

in mixing with tne same pancreatic infusion that of a contracted and anæmic spleen, in order to observe whether it would have the same effect as that of the spleen dilated and engorged with blood. Artificial digestions actually carried out with these infusions gave enormous differences: whereas the pancreatic infusion alone, or that mixed with infusion of contracted spleen digested nothing or almost nothing, the same pancreatic infusion to which had been added infusion of engorged spleen digested rapidly and copiously; indeed, it had often completely digested its dose of proteid by the time that the other two, if digesting at all, had barely commenced. The mixed infusions thus behaved in the same way as a pancreatic infusion taken at the culmen of digestion.

"A large number of similar experiments were made with aqueous boric and glycerin infusions, each being double: *i.e.,* performed in two separate series of vessels, the one containing finely divided fibrin and the other equal-sized cubes of coagulated albumin. The results were always the same. . . .

"At the German Congress of Medicine held at Strasburg in 1886 Herzen exhibited several graduated flasks containing the residua of fibrin and albumin in a number of his digestions, the digesting liquid having been decanted and replaced by alcohol. The physiologists who examined them all recognized that the difference between the residua left by the pancreatic infusions alone and those of the mixture of the pancreatic and splenic infusions were very obvious. In a private conversation with Herzen, however, Heidenhain made the following criticism: It is well known that the pancreatic zymogen is very greedy of oxygen; on the other hand, the spleen during its dilation is engorged with blood. The splenic infusions exhibited were intensely colored by dissolved hæmoglobin—*ergo,* the undoubted and considerable acceleration in digestion obtained by adding such a liquid to another containing trypsinogen could be quite simply explained by the rapid oxidation of the zymogen at the expense of the hæmoglobin. This objection disconcerted Herzen in no inconsiderable degree, and he lost no time in making it the subject of experimental inquiry. He at length succeeded in disproving it by the following excellent experiment: The pancreas of a normal fasting dog

was infused in pure glycerin and the infusion was divided into eight equal portions. These eight portions were mixed with eight samples of blood received directly into a double volume of glycerin, of which four came from a fasting dog and four from a dog in full digestion with the spleen greatly dilated. The four samples were taken in both animals from (1) the femoral artery, (2) the femoral vein, (3) the splenic artery, and (4) a large splenic vein. The eight portions were then given the usual dose of fibrin and placed at a temperature of 40° C. Now, it is evident that the femoral and splenic arterial blood of the two animals contained more oxygen than their venous blood; the former, then, according to Heidenhain, should exercise a powerful influence on the digestion, equal in the two dogs. On the other hand, according to Herzen, the splenic venous blood alone should exercise this influence and especially that of the digesting animal. The result of the experiment was as follows: After one hour there was still no trace of digestion under the influence of the femoral blood, arterial or venous, nor of the splenic arterial blood of the fasting dog; first traces of digestion were beginning to manifest themselves under the influence of the splenic venous blood of this animal. Digestion was rather advanced in the case of the femoral arterial and venous blood and splenic arterial blood of the digesting dog; the fibrin had almost entirely disappeared under the influence of the splenic venous blood of the same animal.

"The answer could not be clearer: the product of the internal secretion of the spleen, borne therefrom by the circulating blood, is present during the period of the dilation of the spleen in feeble, but appreciable, quantity in the blood of the general circulation and abundantly in the splenic venous blood. The venous blood returning from the contracted spleen only contains it in very small quantities. This experiment, several times repeated, always gave the same result, showing that it is not the blood as such which favors the transformation of pancreatic zymogen into trypsin, but that, by picking up from the spleen the unknown substance possessing this property, the blood becomes its vehicle and means of communication with the pancreas.

. . . . . .

"From the bulk of evidence collected by Herzen there thus seems to be very little room for doubt that, apart from hæmatopoietic, and possibly allied, functions possessed by the spleen, the organ furnishes a product of 'internal secretion' which causes in the pancreas the transformation of its inert zymogen into active trypsin."

Bellamy closes his article with a review of the criticisms to which the researches of Schiff and Herzen have been submitted. In the experiments of Lussana, in 1868, the spleens of three dogs were removed and the animals were subsequently killed to ascertain whether the extract of their pancreas would digest coagulated albumin. The pancreatic infusion of the glands of two of the dogs digested 0.25 gramme of albumin in 24 hours; that of the third digested 1.10 grammes in the same period of time. "The latter animal had, however, been killed three hours after a meal: *i.e.*, at a moment when, even had it been in possession of its spleen, that organ would not yet have commenced to become congested. The experiment, therefore, gave the result which might be expected,—viz.: no digestion,—for nobody would accept seriously the digestion of 1.10 grammes, knowing that the pancreas of a dog when digesting can dissolve from 50 to 60 grammes of albumin. . . ." Indeed, the experiments of Lussana appear to us to be confirmatory of Schiff's and Herzen's views.

Carvallo and Pachon also reported negatively, but, errors in their experimental procedures having been brought to their attention by Herzen, subsequent experiments caused Pachon and a new collaborator, Gachet, to reach the conclusions sustaining the views of Schiff and Herzen to which we have referred on page 368. "Nay, they did more," says Bellamy; "they invented an entirely new experiment, at once original and ingenious, which consisted in realizing *in vivo* what Herzen had hitherto only done *in vitro*. This experiment was as follows: A dog, which a long time previously had undergone splenectomy, was anæsthetized and half its pancreas was removed and immediately infused; at the same time a normal dog, in the height of digestion, was killed and its congested spleen was infused in water, and this infusion was injected into the venous system of the spleenless dog; from 15 to 20

minutes afterward the remaining half of the pancreas of the latter dog was infused exactly like the first; of the two infusions when given fibrin and albumin, the second only digested rapidly and copiously."

The investigations of Popelski are next reviewed. "In both normal and splenectomized cats," says Bellamy, "he collected the pancreatic juice by means of a cannula introduced into the duct of the gland, and was unable to find any difference in digestive activity. As, however, his cats had been fasting since the day before, his experiments were made outside the digestive period during which the spleen, becoming congested, furnishes abundantly its product of internal secretion which transforms rapidly and copiously the zymogen into trypsin." . . . "But Popelski also performed some analogous experiments on a dog with a permanent pancreatic fistula, made according to the method of Pawloff. The pancreatic juice of this animal was several times collected and examined before and after splenectomy without any difference in activity being demonstrable. This result, however, elicits no surprise in view of the fact that in both instances the juice was always collected immediately after a meal—*i.e.*,—again to repeat it—in advance of that digestive period during which the spleen enters into function and the pancreas abounds in trypsin; so that as well in this experiment as in that with his cats, Popelski was placed in that position in which the presence or absence of the spleen was a matter of perfect indifference. . . ." The discussion of the various features in point have led to considerable acrimony, but the impartial observer cannot fail to consider that the position of Herzen, of those reviewed, is the only tenable one.

In an article written since Bellamy's review was published Popelski[11] reiterates his views, and states that since it has been demonstrated that there exist in the organism *bodies in the nature of ferments possessing oxidizing properties*, which he believes to be derived mainly from leucocytes, the results obtained by Schiff, Herzen, Pachon and Gachet can all be explained by their action. During the height of digestion

[11] Popelski: Vratch, Feb. 3, 1901.

digestive leucocytosis prevails, and, an accompanying destruction of these cells yielding more oxidizing bodies, the latter, he thinks, are the source of conversion of protrypsin or trypsinogen into trypsin, which thus becomes a function of the blood. Thus, the spleen would have nothing to do with the process, the hyperæmia and dilation of this organ during the formation of trypsin being regarded merely as concomitant phenomena.

The only feature of interest to us in Popelski's last paper is the fact that his experiments were performed in accordance with the directions of Schiff. That he should be driven thereby to ascribe all the phenomena witnessed to the action of "oxidizing bodies" adds materially to the data contributed by Schmiedeberg, Jaquet, Abelous and Biarnés, and Salkowski, proving experimentally the existence of an oxidizing substance, and is suggestive. Indeed, when, in addition to this, we realize the strength of Heidenhain's position, the manner in which it shook to its very foundation the equally strong position of Schiff's views as developed by Herzen, by pointing to *the influence of oxygen* as another agency through which trypsin could be developed from trypsinogen, "trypsin being oxidized trypsinogen," the following query suggests itself: Are we not dealing with two processes working in sequence, a part of the trypsinogen secreted in the splenic vein being converted by the splenic secretion for use in the portal vein, and the rest being converted, when the arteries are reached, by the oxidizing substance?

To determine whether such a deduction is at all warranted or whether it is subject to modifications through which the various views submitted and our own can be conciliated, we find it necessary to closely analyze the manner in which the pancreas and the spleen are functionally governed.

THE FUNCTIONAL MECHANISM OF THE PANCREAS.—The pancreas will first receive our attention. Referring to this organ, Howell says: "Until recently little direct evidence had been obtained of the existence of secretory nerves. Stimulation of the medulla was known to increase the flow of pancreatic juice and to alter its composition as regards the organic constituents, but direct stimulation of the vagus and the sympathetic

nerves gave only negative results. Lately, however, Pawlow and some of his students have been able to overcome the technical difficulties in the way, and have given what seems to be perfectly satisfactory proof of the existence of distinct secretory fibers comparable in their nature to those described for the salivary glands. The results that they have obtained may be briefly stated as follows: Stimulation of either the vagus nerve or the sympathetic causes, after a considerable latent period, a marked flow of pancreatic secretion. The failure of other experimenters to get this result was due apparently *to the sensitiveness of the gland to variations in its blood-supply.*[12] Either direct or reflex vasoconstriction of the pancreas prevents the action of the secretory nerves upon it. Thus, stimulation of the sympathetic gives usually no effect upon the secretion, because vasoconstrictor fibers are stimulated at the same time; but if the sympathetic nerve is cut five or six days previously, so as to give the vasoconstrictor fibers time to degenerate, stimulation will cause, after a long latent period, a distinct secretion of the pancreatic juice."

The quotation almost suffices to show that the sympathetic fibers are vasoconstrictors as elsewhere, in the light of our views, and that the secretory nerve is the vagus. This view is conclusively supported, however, by evidence from other directions. As to the vagus, François-Franck and Hallion[13] in addition to the dilator effects produced on the liver state that "this vasodilator action is also found in the pancreas." Stimulation of the peripheral ends of both vagi, after section, between the cardiac plexus and the diaphragm caused a wide dilation of the pancreatic vessels, which persisted some time, entailing a lowering of the aortic pressure. They also obtained dilation of these vessels reflexly, by stimulating the central end of the nerve after it had been cut on a level with the œsophagus. We have also in the experiments of Mette[14] and Kudrewetzky[15] evidence of the direct action of vagal stimuli upon muscular fiber. Having observed that the secretion caused by stimulating

[12] All italics are our own.
[13] François-Franck and Hallion: *Loc. cit.*
[14] Mette: Archiv f. Physiol., Suppl. Bd., 1894.
[15] Kudrewetzky: *Ibid.*

one vagus could often be arrested by exciting the other vagus, he concluded that this nerve contained antagonistic fibers. This dual set becomes unnecessary, however, if stricto-dilation is accepted as the mechanism of the vasodilation observed by François-Franck and Hallion. Indeed, vagal stimuli capable of causing contraction of the vascular *muscles* to which stricto-dilation is due, can as well induce contraction of the muscular coats of Wirsung's duct, and thus arrest the flow of secretion of pancreatic juice precisely as it does that of bile.

As the sympathetic supply François-Franck and Hallion[16] obtained plethysmographically vasoconstrictor effects on stimulating the splanchnic, and traced the constrictor fibers to the cord. The fibers were supplied through the fifth thoracic communicating branches to the second lumbar inclusive, the majority of them reaching the solar plexus by way of the greater splanchnic. The fibers then formed, they contend, "a secondary plexus enveloping the pancreatic artery." They also state that "this arterial path seems to be the only one, since the destruction of the fibers that accompany the artery suppress the pancreatic vasoconstrictor effects of any sympathetic branch stimulated." Again, Popelski[17] refers to various ways in which inhibition of the flow of secretion may be caused. Among these are: Stimulation of the vasoconstrictor fibers, and stimulation of "secretion-inhibiting" fibers supposed by him to represent a special set. The mode of termination of the sympathetic fibers on the pancreatic artery as given by François-Franck and Hallion readily accounts for the inhibition caused by excessive excitation of the nerves. These (sympathetic) fibers are thus evolved from the suppositious special "secretion-inhibiting" nerves—a rather incongruous combination, since by arresting the flow of blood to the organ, they prevent and may arrest the secretory process.

It is evident that these vasoconstrictor fibers are distinct from the true secretory fibers, for Pawlow[18] says, alluding to Popelski's work: "By a careful preparation of the nerves,

[16] François-Franck and Hallion: Archives de physiol. norm. et pathol., T. ix, p. 661, 1897.
[17] Popelski: Centralbl. f. Physiol., Bd. x, S. 405, 1896.
[18] Pawlow: "The Work of the Digestive Glands," Eng. Trans., London, 1902.

some branches were discovered whose excitation caused a secretion without any latent period almost as promptly as the chorda expels saliva. From the latter fact we must conclude that in the branches mentioned, the secretory fibers of the pancreas have been anatomically separated from the inhibitory." Finally, a proof that we are dealing with exaggerated constriction ending in experimental inhibition and not with a true secretory nerve is afforded by the following observation of Kudrewetzki's[19]: "If the sympathetic nerve be excited by means of an induced current, a gentle intermittent advance of the secretion is observed, but only during the first few seconds; during the later stages of the excitation, and after its stoppage, the secretion is completely arrested." We have here, obviously, the identical result observed in the submaxillary gland when the cervical sympathetic is stimulated—a brief exacerbation of activity due to the propulsion of a small quantity of blood into the secretory elements—and simultaneously additional evidence that the sympathetic in the pancreas fulfills vasoconstrictor functions.

This involves the conclusion that as elsewhere the blood-plasma—laden with oxidizing substance—is able to reach the glandular cells. This is shown by a brief review of the relationship between the nervous and vascular structures of the organ.

Referring to the blood-vessels, Piersol says: "The larger arterial branches run within the interlobular connective tissue, sending off vessels which pass between the lobules and supply the glandular parenchyma with twigs. These latter enter the lobules and form *net-works which inclose the individual acini within the capillary reticulum*. The capillaries lie beneath the basement membrane in close relation with the glandular epithelium. The veins accompany the arterial trunks within the connective tissue." A similar arrangement prevails in the distribution of the nerve-terminals. According to Ramón y Cajal and C. Sala, the pancreas contains many nerve-cells and fibers of Remak. Some cells are found in the interacinous spaces; others are in contact with the intrinsic vascular walls, and *their finer prolongations surround the glandular cells.*

[19] Kudrewetzki: Quoted by Pawlow: *Loc. cit.*

Those connected with the vessels *form a plexus around them,* and send extremely fine filaments to the muscular elements. Alluding to the nerve-cells, Ramón y Cajal says: "We may consider this cell as a special cell, all the prolongations, or almost all the prolongations, of which possess the meaning of nervous prolongations *contrary to the cells of the sympathetic chain,* that have two kinds of prolongations: along one, or fiber of Remak, for the viscera, and short prolongations comparable to the protoplasmic prolongations of cerebro-spinal cells, destined to establish relations by contact between the neighboring cells of a ganglion." Berdal, who quotes the above, therefore recognizes two varieties of nerve-fiber in the pancreas: "1. The nerve-fibers formed by the cellular prolongations and which supply the periacinous and perivascular plexuses. 2. The nerve-fibers derived from the sympathetic nerves which penetrate into the pancreas *with the vessels.*

On the whole the functions of the pancreas appear to be governed as follows:—

1. The nervous supply of the pancreas is derived from the vagus and the sympathetic systems.

2. When the secretory functions of the organ are to be enhanced, the vagal terminals cause vasodilation of its arterioles, thus increasing the arterial blood circulating through it.

3. When the functional activity of the pancreas is to be diminished its arterioles are caused to contract by the sympathetic nerves, and the blood circulating through the organ is reduced.

FUNCTIONAL MECHANISM OF THE SPLEEN.—The innervation of the spleen includes, as a predominating feature, the distribution of a fair proportion of the terminal fibers to the muscular elements, which, in man, are mainly supplied to the trabeculæ. "We have evidence," says Professor Foster, "that the muscular activity of the spleen, whether of the muscular capsule and trabeculæ and arteries combined, or of the latter alone, is under the dominion of the nervous system. *A rapid contraction* of the spleen may be brought about in a direct manner by stimulation of the *splanchnic or vagus nerves,*" . . . "it may also be caused by stimulation of the *medulla oblongata* with a galvanic current or by means of *asphyxia.* Though the