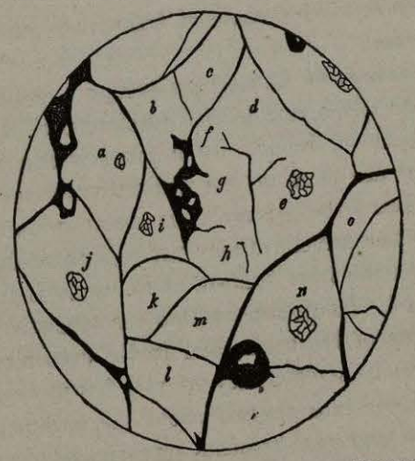
glomerulus of tortuous, freely-anastomosing vessels, much thicker than those between the acini. A single afferent vessel like that of the glomerulus of the kidney does not enter this group of dilated capillaries, but numerous anastomoses make it continuous with the interacinar capillaries. When Berlin blue is injected through the aorta into the arteries of the pancreas, it not infrequently happens that in portions of the gland which are poorly injected the vessels of the island



CAMERA-LUCIDA TRACING OF THE LOBULE BOUNDARIES IN ONE OF A SERIES OF SECTIONS FROM THE SPLENIC END OF A CAT'S PANCREAS.

The majority of the lobules are well defined. Those marked *d*, *e*, *f*, *g*, and *h* are poorly outlined, but are found to be more readily distinguishable when traced through the series of secretions. The lobules, which are lettered (*a* to *o*), were traced through the series, and each was found to contain an island of Langerhans situated near its center. The section passes through the island in lobules *a*, *e*, *i*, *j*, and *n*. (*Eugene L. Opie.*)

are filled with the injected mass, while the surrounding capillaries are, for the most part, empty. If instead of soluble Berlin blue a granular injection mass—for example, cinnabar or ultramarine blue—is used, the islands may be injected, while the interacinar capillaries contain little of the injected material. The glomerular net-work is in very free communication with the smallest arteries, and apparently has a richer blood-supply than other parts of the lobule.

"In the human pancreas lobules and lobule groups are not so regularly arranged as in the cat. But both structures are more or less clearly definable. The lobules vary much in size, and are usually not clearly separated from one another. Though an island of Langerhans is often situated in the center of a more or less clearly defined lobule, no constancy of position is discoverable. The lobule groups are separated by relatively wide bands of loose areolar tissue in which are contained the medium-sized ducts, the blood-vessels, and the nerves. Within a lobule group the arteries and veins, which are side by side, do not, as in the cat, accompany the ducts."

The multiplicity of facts reviewed in the foregoing pages and the intricacy of the whole question make it necessary to collate and group in logical sequence the salient features of each subject discussed, in order to render a fruitful comparison of their merits possible. Not only are we required to analyze the questions involved in the light of the solid data that the last forty years have furnished,—*i.e.*, since Schiff first studied the relations between the spleen and the pancreas,—but all these must likewise be sustained by, and be in accord with, the functional mechanisms of the organs involved as I interpret them if my own views are well founded. If they are, they must necessarily assist us greatly in elucidating the various problems, physiological and pathological, to which reference has been made, since the very elements which they introduce bear upon a predominating factor in all these processes: *i.e.*, oxidation. To this subdivision of the subject we will, therefore, turn our attention.

Can we ascribe to oxygen, or rather to the oxidizing substance of the blood, the conversion of pancreatic trypsinogen into trypsin? We have seen that in both the spleen and pancreas the oxidizing substance seems, as elsewhere, to play the main functional rôle; the extrinsic and intrinsic vessels are disposed in a similar manner as regards their nervous relations, and vasodilation calculated to increase the flow of blood through both organs is similar. Moreover, we have seen that in the spleen the dilation incident upon malarial intoxication could be traced to the adrenals,—the primary source of excessive oxidation,—while in toxic glycosuria we obtained

as clear evidence that overactivity of the pancreas could also be ascribed to these organs. Again, the ease with which oxygen is thought to convert trypsinogen into trypsin—a mere current of oxygen through a solution of zymogen sufficing to produce trypsin—has been fully emphasized. Besides Heidenhain's labors in this connection, we need but recall Schiff's experiment with the two halves of a pancreas, one of which was infused at once and the other left exposed to the air a day, with the result that the latter alone proved active; and also that of Herzen, in which an infusion of active spleen mixed with an infusion of inactive (hence zymogen-laden) pancreas proved very active, while a pancreatic infusion mixed with one of inactive spleen digested nothing. Heidenhain ascribed to oxidation the conversion into trypsin, in this experiment. Indeed, when we consider the wealth of oxygen in the blood supplied the pancreas, direct from the lungs via the cœliac axis, it would seem as if it should be the predominating factor of the conversion processes involved.

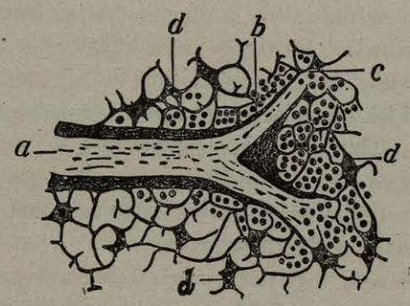
And yet, the oxidizing substance being a constituent of the blood-plasma, it would have to penetrate into the ducts *per se* and *as* oxidizing substance in order to carry out the required reaction. There is no evidence that a direct channel, such as there is in the spleen, by means of which the capillaries directly pour their blood into the secreting structures, exists. As may be seen in the annexed illustration, the splenic vessels actually terminate in the latter; "their walls become much attenuated, lose their tubular character, and the cells of the lymphoid tissue of which they are composed become altered, presenting a branched appearance and acquiring processes which are directly connected with the processes of the sustentacular cells of the pulp."[33]

Nor is there evidence that canaliculi such as those of the hepatic cell exist by means of which the blood-plasma or its contents may directly find their way to a structure corresponding to bile-channels, which in the pancreas would be represented by the ducts. Langerhans long ago demonstrated that canaliculi were present in the lobules between the epithelial

[33] Pickering Pick and Howden: "Gray's Anatomy," 1901.

cells, but these, besides being pyriform, terminate as blind pouches, with their orifice directed toward the glandular lumen. Saviotti also found these minute, delicate, pouch-like channels. Ramón y Cajal, using the Golgi method, found that they sent offshoots into the cells themselves, but that these also ended as blind pouches, their ampullar dilations never reaching beyond the line which separates the granular portion of the cell from the clear area. It is evident that these constitute collecting channels for the products of glandular metabolism: a further indication that no free channel between the blood-stream and the ducts exists.

Indeed, experimental proof to this effect is available: When the histological examinations of Kühne and Opie were



TERMINATION OF SMALL BLOOD-VESSELS IN THE SPLEEN. (*Gray.*)
a, Small artery. *b*, Vessel undergoing lymphoid change. *c*, Vessel continuous with supporting cells. *d*, Supporting cells.

mentioned on page 394, it was noted that material injected into the *duct* of the gland did not penetrate the islands of Langerhans. If, on the other hand, Opie's observation that injections of Berlin blue often filled the vessels of the island *per se*, leaving the majority of surrounding capillaries empty, is considered in this connection, it is evident that there can be no direct communication between ducts and blood-stream through either the islands of Langerhans or the glandular lobules that contain them. This involves an all-important deduction, however, viz.: that the splenic ferment, as well as the oxidizing substance, merely passes through the pancreas in transit, the latter, in its usual capacity of reagent, being intended only to activate function.

But how, under these circumstances, can we account for the experimental results reached by Schiff and Herzen, Heidenhain, Lépine, Pachon and Gachet, and Popelski? All these observers in one way or another have unquestionably shown a direct relationship between the blood-serum and trypsinogen, Heidenhain and Popelski considering oxygen as the converting agency, with solid experimental data to sustain them; Schiff, Herzen, and the other investigators mentioned attributing to the splenic ferment the same mission, with equally strong experimental backing. How account, for example, for the results observed in the following experiment of Herzen's? Two fasting dogs, having received all the meat they could eat, were at once submitted to ligation of the pylorus, bile-duct, and jejunal end of the duodenum, and also, in one of the dogs, of the hilum of the spleen. Albumin having been introduced into the duodenum, both dogs were killed after seven hours. In the dog with ligated splenic hilum the albumin was intact; in that in which the splenic vessels were free, the albumin had disappeared. This and other experiments to which we have referred may, indeed, be said to prove—whichever be the prevailing converting agency—that a communication between the blood-channels and the ducts exists.

We have seen that there is no evidence to show that the acini in direct communication with the ducts also open into the blood-vessels; these, as elsewhere, form a close-net-work around the acini, but they do not open into the blind pouches of the latter. Could the communicating channels traverse the islands of Langerhans? That these organs do not possess such channels or even ducts has been shown by Dogiel,[34] who studied this question in a well-preserved human pancreas treated by the chrome-silver method, and in which the gland-ducts, "even in their finest intra-alveolar branches, were well stained." Yet these structures possess morphological characteristics that are suggestive. Dogiel, for example, found that they possessed relatively large capillaries located in the cellular trabeculæ. All investigators seem to agree upon the unusual size of those vessels. Kühne and Lea define the islands as "glomerular

[34] Dogiel: Böhm and von Davidoff, *Loc. cit.*

structures composed of *dilated* and tortuous capillaries." Opie calls them "vascular islets" which are in "very free communication with the smallest arteries and apparently have a richer blood-supply than other parts of the lobule." That these dilated arteries are possessed of special functions is suggested by the fact that, "if, instead of a solution of Berlin blue, *a granular* injection mass—for example, cinnabar or ultramarine blue—is used, the islands may be injected, while the intra-acinar capillaries contain little of the injected material." They appear to constitute alveoli or ampullæ rather than true vascular channels, in which what blood passes through them is submitted to some kind of process.

An interesting feature in this connection was noted by Opie, viz.: the fact that the cells of the islands of Langerhans are in some instances continuous with the regular glandular elements of the organ, in such a manner as to prolong the ducts of the latter by encircling them. "Occasionally," says the author, "one sees, apparently within the islands, cells arranged, as in the acini, about a central lumen, and, indeed, in many instances, it is difficult to convince one's self that they do not form part of it." This intimate relationship between the two sets of glandular elements is further emphasized by the manner in which their capillaries are related. While the smaller arteries or arterioles ramify between the lobules and supply the net-work of capillaries to the acini, they also communicate with the tortuous and dilated vessels of the islands of Langerhans; so that the latter, as regards their vascular relations, really constitute glomerular expansions and offshoots of the regular acini's blood-channels. We thus have two sets of superposed glands around a common duct, the upper, or common acini, pouring their own secretion (or granules) into it through their microscopical ducts; the lower, those of the islands—possessed of no ducts or other orifices—presenting their dilated capillaries or alveolar walls so as to cause them to face, and perhaps slightly project into its lumen. If we now replace by an active circulation through all these vessels the cinnabar or ultramarine-blue injections referred to above, the accumulation of the latter in the islands distinctly points to a similar process during life: *i.e.*, accumulation of blood and

its normal result (with narrower blood-vessels at each end of the glomerulus): *i.e.*, centrifugal pressure.

If we now conjoin Opie's remark—"the impression is produced that the columns of the island are in continuity with cells having an acinar arrangement"—and Mall's observation, in his study of the microscopical anatomy of the spleen,—that "the ampullæ and venous plexus have very porous walls which permit fluids to pass through with great ease . . ."—it seems probable that we hold the key to the situation. Indeed, what have we in the dilated glomerules of capillaries of the islands of Langerhans but vascular ampullæ? Centrifugal pressure under the circulatory conditions mentioned can have but one result: *i.e., filtration of the blood-fluids through the ampullar walls and into the ducts.*

It is, perhaps, unnecessary to point to the fact that, besides being the only functional mechanism warranted by the anatomical structures present, it also meets all the requirements of the well-founded experimental data adduced. The precision with which it seems to harmonize the two seemingly antagonistic features of the general function represented—*i.e.*, the Schiff-Herzen spleno-pancreatic process and the Heidenhain zymogen-oxidation process—is also noticeable. If it is also realized that all these elements of the general function now fall sequentially in the normal order of their physiological usefulness, it will become apparent that I must have reached a solution—that submitted below—worthy of confidence:—

1. The splenic ferment secreted into the splenic vein is carried to the portal vein and by this vessel through the liver, thence by the hepatic vein to the inferior vena cava, and after passing through the cardiopulmonary circuit is distributed throughout the entire organism.

2. The quantity of splenic ferment distributed to the pancreas is proportionate to the amount of blood carried thereto by the pancreatic subdivisions of the splenic artery, and represents but a fraction of that supplied to the general circulation.

3. The splenic ferment distributed to the pancreas follows the course of its blood-channels, and is distributed to the cellular elements of the organ dissolved in the blood-plasma.

4. On reaching the cellular elements, the plasma, through its oxidizing substance (adrenoxidase), insures functional metabolism of both glandular structures present,—the lobular acini and their immanent structures, the islands of Langerhans,—which metabolism, during the passive, or inactive, state of the organ, ends in the formation of the secretion granules.

5. When at the end of the fourth hour of general digestion the pancreatic ferments are required in the intestinal canal, the vagus incites, sustains, and governs the functional activity of both the pancreas and the spleen, and thus insures their synchronous action as long as the pancreatic ferments are needed.

6. Intrinsic-nerve (vagal) dilation of the arterioles that supply both the pancreatic lobules and the islands of Langerhans with capillaries constitutes, as elsewhere, the mechanism through which glandular activity is sustained; but, the islands' vascular ampullæ possessing no muscular layer, they become the seat, owing to their large size, of sufficient blood-pressure to cause the blood-plasma and its contained splenic ferment and oxidizing substance (adrenoxidase) to filtrate through their walls.

7. Some lobules are entirely composed of true secreting cells; others contain, besides, islands of Langerhans. In the latter lobules the secretion, therefore, consists of two different bodies: the granules of the true secreting cells and the blood-plasma derived by filtration from the islands.

8. The true secreting cells and those of the island being in continuity and surrounding a common lumen (Opie), both bodies—(1) the zymogen, or trypsinogen-forming, granules, and (2) the plasma containing the splenic ferment and the oxidizing substance (adrenoxidase) meet in this common lumen, which connects with the terminal ramifications of the pancreatic duct.

This is about as far as we can proceed at present, since we can only surmise that, as soon as the products referred to meet in the glandular lumen, the splenic ferment at once converts the trypsinogen granules into liquid trypsin. Interesting in this connection, however, is the fact, observed by Laguesse, that "long before the pancreas begins its functions as a digestive gland granules accumulate in the internal zones of the cells; and when these come into contact with the blood a portion of them appears as though dissolved." As is well known, this is precisely what happens even in true acini that do not belong to

lobules supplied with islands. When secretory activity occurs, the granules of the inner zone of the cells simply disappear in the central lumen; but how and in virtue of what agency they are transformed into secretion at this point has not been determined. In the lobules supplied with islands of Langerhans the effused serum more than satisfies this feature, since it supplies two agencies thought to be capable of converting the granules into trypsin; but what of the lobules deprived of islands? How are *their* granules converted?

To answer these questions we must first ascertain which of the ferments credited to the pancreas can be shown to originate in the true acini. We have seen that, when the hilum of the spleen is ligated and no splenic ferment can find its way to the blood, the digestion of albumin ceases. It is, therefore, evident that, in accordance with Herzen's view, the splenic ferment is a *sine qua non* in the process through which trypsinogen is converted into trypsin. But why does the oxidizing substance not continue the conversion after ligation of the splenic hilum? There is but one answer to this, viz.: Herzen's zymogen and trypsinogen are not similar bodies; while zymogen is converted into some pancreatic ferment by oxygen, trypsinogen is not, and always requires the splenic ferment.

To illustrate this fact we submit, *in extenso,* two of Gachet and Pachon's experiments, performed to show that it was the spleen's ferment, and not its hæmoglobin, that converted protrypsin, which they term "proferment." Believing that zymogen, which, as shown by Heidenhain, is very greedy for oxygen, and "proferment" are the same bodies, their aim is to prove that, injected in arterial blood, pancreatic ferments cannot be converted into trypsin therein. But, interpreted from our standpoint, — since the blood contains oxidizing substance which zymogen would readily take up, — these experiments prove that zymogen and their proferment (trypsinogen) differ, as stated.

"As the proferment of the pancreas becomes very easily transformed into trypsin under the influence of oxygen," say Gachet and Pachon, "it seems possible that splenic extracts, intensely colored by the hæmoglobin, should owe their trypsinogenous power to the fixed oxygen of hæmoglobin which

they hold in solution. If such is the case, arterial blood, richer in oxygen, should render a pancreatic infusion containing the proferment more active than venous blood. A. Herzen has already studied this question and antagonized it by means of appropriate experiments. On our side, we have tried to ascertain the value of this opinion in the following manner:—

"*Experiment II.*—The pancreas of a fasting dog was allowed to macerate two hours in ten times its volume of a saturated solution of boric acid. By decantation, 200 cubic centimeters of the maceration liquid were taken and distributed among four flasks: A, B, C, and D.

"To A were added 20 cubic centimeters of defibrinated *arterial* blood (obtained from the fasting dog).

"To B were added 20 cubic centimeters of defibrinated venous blood (obtained from the fasting dog).

"To C were added 20 cubic centimeters of *congested* spleen (aqueous maceration).

"To D were added 20 cubic centimeters of distilled water.

"These flasks, in each of which was introduced 1 cubic centimeter of albumin, were then placed in the oven at 39° C.

"At the end of 4 hours beginning digestion was observed in flask C; villosities appeared on the surface of the cube of albumin, which continued to be attacked in an energetic manner.

"A and B, after remaining in the oven 24 hours, did not show very clear traces of digestion. Their cubes of albumin presented slightly less sharp projections, and their angles were more rounded. The cube in flask D was slightly attacked.

"*Experiment III.*—The pancreas of a fasting dog was divided into three parts and triturated: the first alone; the second with 20 cubic centimeters of femoral arterial blood; the third with 20 cubic centimeters of venous blood, taken, as was the former, from a fasting dog. These were placed in flasks A, B, and C, containing each 150 cubic centimeters of boric-acid solution. After remaining 2 hours in the oven the peptonizing power of the decantation liquids was tried. Their proteolytic action was very slow; the first signs of digestion had appeared: in A after 16 hours of oven; in B and C after 20 hours. Digestion was not further advanced in the flask

containing arterial blood than it was in that containing venous blood.

"It can be seen that in these two experiments arterial blood showed itself as inactive as venous blood. One cannot, therefore, ascribe the unquestionable action of the extract of congested spleen upon the pancreatic proferment to the oxygen of splenic tissue."

There is one feature in this connection, however, which requires elucidation: the influence that the use of *fasting* dogs might have had on the experiments. We have seen that under these conditions suprarenal activity becomes reduced; the blood may, therefore, contain but a minimum of oxidizing substance. Herzen performed an experiment which not only confirms our conclusion that zymogen and trypsinogen are not identical bodies, but also shows that fasting does not influence the results just given. As Herzen's experiment has already been reviewed at length, we will only reproduce its salient points. The pancreas of a fasting dog (hence rich in trypsinogen and other ferment-forming agencies) was infused in glycerin, and this in turn was mixed with eight samples of blood (bled directly in double its quantity of glycerin), four being taken from a fasting dog and four from a dog in full digestion with its spleen greatly dilated. The four samples were taken in both animals from the femoral artery, the femoral vein, the splenic artery, and the splenic vein. Fibrin was then added to each sample. "After 1 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." This seems to us to confirm not only the view held by Herzen, that the splenic ferment is the only agency capable of converting trypsinogen into trypsin, but also that trypsinogen does not, like zymogen, possess affinity for oxygen.

This may be further demonstrated by showing that oxygen does exist in the blood, and that if we were dealing with zymogen it would be oxidized therein. The oxidation of sugar converted from glycogen, we have seen, represents the main factor in the production of functional energy in the muscles and other structures. That sugar occurs in the blood normally, but in small quantities, its combustion therein depending mainly—as in toxic glycosurias—upon suprarenal activity, we have also seen. The more these organs produce of their secretion, the greater is the proportion of oxidizing substance in the blood, and suprarenal insufficiency means a corresponding increase of sugar in the blood through imperfect oxidation. Hence the oxidizing substance is a sugar-destroying agency.

That an agent capable of consuming sugar exists in the blood was ascertained by Lépine in 1889, who named it "glycolytic enzyme." Howell, referring to this substance, says: "It has been asserted by Lépine and Barral that there is normally present in the blood an enzyme capable of destroying sugar. Their theory rests upon the *undoubted fact that sugar added to blood outside the body soon disappears.*" This obviously constitutes another proof of the existence of oxidizing substance in the blood.

Howell, referring also to the supposed source of Lépine's glycolytic enzyme, says, referring to the pathogenesis of glycosuria: "The most plausible theory suggested is that the internal secretion produced contains a special enzyme, glycolytic enzyme, whose presence in the blood is necessary for the consumption of sugar. Such an enzyme *may be obtained from the blood,* but it is not proved whether it is a normal constituent or whether it is produced after the blood is shed by the disintegration of some of its corpuscular elements." . . . "It is interesting and suggestive to state, in this connection, that post-mortem examination in cases of diabetes mellitus in the human being has shown that this disease is associated in some instances with obvious alterations in the structure of the pancreas." That the glycolytic enzyme is, as oxidizing substance, a normal constituent of the blood is obvious; but the interesting feature to determine now is whether, as believed by Lépine, the pancreas is the source of the ferment, since, if it