matter has not yet been fully worked out, we have already sufficiently clear indications that the flow of blood through the spleen is, through the agency of the nervous system, varied to meet changing needs. At one time a small quantity of blood is passing through or is being held by the organ and the metabolic changes which it undergoes in the transit are comparatively slight. At another time a larger quantity of blood enters the organ and is let loose, so to speak, into the splenic pulp, there to undergo more profound changes, and afterward to be ejected by rhythmic contractions of the muscular trabeculæ."

That rapid contraction of the spleen should occur under stimulation of the splanchnic nerve is easily accounted for when the rôle of sympathetic nerves—those it supplies the organ—is considered to be that I have attributed to them in the foregoing chapters: that of vasoconstrictor. Indeed, it is plain that under stimulation these nerves should reduce the caliber of the arterioles, and, therefore, the volume of blood admitted into the organ, and that it should contract rapidly owing to continued depletion of its veins. The constrictive effect of stimulation of the medulla on the arteries we have repeatedly seen; as this is due to contraction of their muscular coats, the spleen is evidently influenced in a manner similar to that following stimulation of the splanchnic, the smallest arteries being the first obstructed under violent vasoconstriction.

But why should stimulation of the vagus also induce splenic contraction? This requires an examination of the distribution of the nerve-terminals. The innervation of the spleen was studied by Kölliker in various animals,[20] and his observations, when viewed in the light of my conception of the functional mechanism of glandular organs, are suggestive. "The vasomotor nerves enter the organ with the large arteries. In the *walls* of the large arteries the main trunks form a well-marked superficial *plexus* with oblong meshes in the adventitia, and a *deep*, more quadrate *net-work* in the tunica media; some end in the little branched arborizations in this coat. The smaller arteries and the trabeculæ receive their nerves from

[20] Kölliker: Sitzungsbericht d. Würsb. Phys. med. Gesellschaft, No. 2, 1893.

the rich maze of fibers in the pulp, consisting of axis-cylinders, which, however, do not anastomose. Other fibers form a plexus on the surface of the trabeculæ, and from this fibrils penetrate *into* the interior of the trabeculæ *(which contain much smooth muscle)* and end by free arborizations." Free terminals, which Kölliker regards as sensory fibers, were also found. When we consider that the trabeculæ penetrate deeply into the interior of the organ from the inner surface of the capsule in every direction, thus forming a spongy frame-work, and that the muscular capsule overlying the organ and this spongy frame-work, is also supplied with vagal nerves, its contraction under the influence of the latter under stimulation also becomes self-evident in the light of our views: The vagus acting as a vaso-dilator allows an excess of blood to penetrate into the muscular elements, causing them to contract and thus to diminish the size of the organ. Indeed Roy[21] who first called attention to the rhythmic contractions of the spleen, ascribed them to impulses received by way of the vagus.

A feature of the experimental work upon this organ which tends greatly to produce confusion in the interpretation of its function, is the belief that it is supplied with inhibitory fibers. Thus, according to Schäfer[22] these fibers are contained in the splanchnic nerves and their stimulation "produces a dilatation of the spleen." It is plain, in the light of our interpretation of "inhibition," that we are merely dealing with an experimental phenomenon due to the excessive vasoconstriction which electricity produces when applied to sympathetic vasoconstrictors, and that the organ does not receive "inhibitory fibers" as text-books call them.

The interpretation of the splenic functional mechanism in accordance with our views is greatly facilitated when the microscopical anatomy of the organ is considered in the light of F. P. Mall's[23] researches. The organ is divided, as is the liver, into lobules, each of which is bounded by "interlobular" trabeculæ: those to which we have already referred. Each

[21] Roy: Journal of Physiol., vol. iii, p. 203, 1880-2.

[22] Schäfer: "Proceedings of Royal Society," London, 1896, vol. lix, No. 365; and Journal of Physiology, 1896, vol. xx.

[23] F. P. Mall: Johns Hopkins Hospital Bulletin, Sept., Oct., 1898.

lobule is about 1 millimeter in diameter, is partitioned into about ten compartments by intralobular trabeculæ, and receives an artery which sends minute branches to each compartment. There is also considerable analogy between each one of these compartments and the hepatic lobule, the hepatic cells being represented by masses of pulp separated by venules, which vessels carry back to the veins leading to the greater splenic vein the various elements transferred to the liver. The pulp itself is made up of an extremely delicate reticulum, in which are found red corpuscles, lymphocytes, remains of corpuscles with or without pigment, etc. The arteries—which bring to the organ oxidizing substance—soon after entering the organ assume an unusual shape: their outer coat becomes lymphoid, forming nodules similar to the solitary follicles of the intestine,—*i.e.*, the Malpighian corpuscles,—in which lymphocytes are formed. When, after numerous subdivisions, their diameter becomes greatly reduced, the arteries resume their normal adventitia and on reaching the pulp in the compartments break up into minute capillaries. The arrangement is, after all, an uncomplicated one, and similar, in general plan, to that of other organs reviewed.

The connection between the nervous supply of the spleen and that of the other digestive organs becomes evident when the distribution of the cœliac-plexus branches is recalled. "The splenic plexus," say Pick and Howden,[24] "is formed by branches from the cœliac plexus, the left semilunar ganglia, and from the right pneumogastric nerve. It accompanies the splenic artery and its branches to the substance of the spleen, giving off, in its course, filaments to the pancreas (pancreatic plexus) and the left gastro-epiploic plexus, which accompanies the gastro-epiploica sinistra artery along the convex border of the stomach." If we append to this Kölliker's description of the intrinsic nervous supply and the manner in which it is connected with the blood-vessels, it will become apparent that we have a counterpart of the vasculo-nervous mechanism of all the other organs of the digestive system we have studied, viz., a system of vagal fibers capable of inciting the spleen to

[24] Pick and Howden: "Gray's Anatomy," p. 806.

increased functional activity by causing an excess of blood to enter the organ, and sympathetic fibers to reduce its functional activity by causing the vessels to resume their normal caliber.

The functions of the Malpighian corpuscles around the vessels would thus be insured by fibers from the vagus. Indeed, Fusari[25] traced nervous filaments within these bodies. The pulp is also possessed of a "rich maze of fibers consisting of axis-cylinders"—doubtless sensory structures. But here an independent motor supply must also be present, since we also have fibers that form "a plexus on the surface of the trabeculæ," filaments from which penetrate *into* the trabeculæ. These, we have seen, contain much smooth muscle, and the nerve-filaments are connected with them by "swellings" (Fusari), evidently end-plates. Kupffer's bile-alveolus, with its canaliculi, is recalled by a similar receptable: *i.e.*, Mall's "intralobular venous spaces," which form the starting-point of the venules that ultimately end in the large trunks leading to the splenic vein.

On the whole, we may conclude as follows:—

1. The nerves of the spleen are derived from two autonomous sources, the vagus, or pneumogastric, and the sympathetic system.

2. The functional activity of the spleen is incited by the vagal nerves distributed to its arterioles: by causing dilation of these vessels, they admit an excess of blood into all the structures of the organ, causing the latter to dilate.

The vasoconstrictor functions of the sympathetic are as evident here as in other organs studied. "The spleen," says Howell, "is supplied richly with nerve-fibers which, when stimulated either directly or reflexly cause the organ to diminish in size. According to Schäfer these fibers are contained in the splanchnic nerves, which carry also inhibitory fibers whose stimulation produces a dilatation of the spleen." The sympathetic supply of the spleen has been clearly shown. Bulgak[25a] obtained vasoconstrictor effects, the organ becoming pale and shrunken, by stimulating fibers which he traced to the semilunar ganglion and thence to the left splanchnic. Tarchanoff

[25] Fusari: Archives Italiennes de Biologie, Turin, vol. xix, p. 288, 1894.
[25a] Bulgak: Virchow's Archiv, Bd. lxix, p. 181, 1877.

reached similar results but by stimulating either splanchnic. Schäfer and Moore studied the same subject by means of a plethysmograph specially constructed to avoid any obstruction to the circulation in the organ's extrinsic vessels. They found the spleen extremely responsive to blood-pressure fluctuations, and obtained constriction by stimulating either splanchnic, the left, however, giving more marked results than the right. The constrictor fibers were found to raise from the third thoracic to the first lumbar inclusive, the most active arising from the sixth, seventh, and eighth thoracic. This evidence clearly shows that the rôle of the spleen's sympathetic supply is purely vaso-constrictor. Hence:—

3. When the functional activity of the organ is to be diminished, the sympathetic fibers cause constriction of the arterioles, thus reducing the volume of blood admitted into the organ and passive contraction of its capsule.

The rôle of the spleen has not been so far clearly established. Howell, in the second edition of his text-book (1907) writes in this connection: "As to the theories of the splenic functions, the following may be mentioned: 1. The spleen has been supposed to give rise to new red corpuscles. This it undoubtedly does during fœtal life and shortly after birth, and in some animals throughout life, but there is no reliable evidence that the function is retained in adult life in man or in most of the mammals. 2. It has been supposed to be an organ for the destruction of red corpuscles. This view is founded chiefly on microscopical evidence according to which certain large amœboid cells in the spleen ingest and destroy the old red corpuscles, and partly upon the fact that the spleen tissue seems to be rich in an iron-containing compound. This theory cannot be considered at present as satisfactorily demonstrated. 3. It has been suggested that the spleen is concerned in the production of uric acid. This substance is found in the spleen, as stated above, and it was shown by Horbaczewsky that the spleen contains substances from which uric acid or xanthin may readily be formed by the action of the spleen-tissue itself. More recent investigations[26] have shown that the spleen, like the liver

[26] Consult Jones and Austrian: Zeit. f. physiol. Chem," Bd. xlviii, S. 110, 1906.

and some other organs, contains special enzymes (adenase, guanase, and xanthin oxydase), by whose action the split products of the nucleins may be converted to uric acid, and it is probable, therefore, that this latter substance is constantly formed in the spleen. 4. Lastly, a theory has been supported by Schiff and Herzen, according to which the spleen produces something (an enzyme) which, when carried in the blood to the pancreas, acts upon the trypsinogen contained in this gland, converting it into trypsin." The latter is treated at length under the next heading.

The statement that the spleen contains, as do other organs, such ferments as adenase, guanase, and xanthin oxydase is suggestive, in view of the fact that they are all oxidizing ferments. This fact is all the more interesting in that, as shown below, it is the plasma alone, *i.e.*, plasma deprived of its red corpuscles which circulates in the intercellular spaces of the pulp-cords.

An incidental remark of Professor Mall's, in the contribution previously referred to, goes far toward demonstrating that I have not erred so far in ascribing to the blood-plasma *per se* the active part in the blood's function. This constitutes such a far-reaching feature of this entire work that the following lines appear to us as timely: "The microscopical anatomy shows that the ampullæ and venous plexus have very porous walls which permit fluids to pass through with great ease and granules only with difficulty. In life *the plasma* constantly flows through the *intercellular spaces* of the pulp-cords, while the *blood-corpuscles keep within fixed channels*. Numerous physiological experiments which I have made corroborate this view." If this can occur in the spleen it is doubtless possible elsewhere in the organism, especially when we consider that red corpuscles average in diameter about $^1/_{3000}$ of an inch, while the lumen of the majority of functional capillaries is less than one-half that size. Of course, corpuscles adjust themselves to the dimensions of the structures surround them; but it is apparent that in many instances—the tortuous capillaries of pericellular net-works, for instance—such a system could but compromise the free circulation of the fluids, and, simultaneously, the functional efficiency of the organ itself.

THE SPLENO-PANCREATIC INTERNAL SECRETION.

From the data already submitted as to the functions of, and the functional relationship between the spleen and pancreas, it is evident that each possesses its own complete mechanism, and that *in both organs, as elsewhere in the economy, the oxidizing substance (adrenoxidase) or the blood containing it is the source of functional activity.*

Still, have we any reason to believe, with Popelski, that it is through oxidation that the intrapancreatic trypsinogen becomes converted into trypsin? Can we say, for instance: the intrapancreatic conversion of trypsinogen into trypsin is not effected by the splenic ferment, but by the oxidizing substance, when the efferent vagus nerves transmit appropriate impulses? We think not, much as such a process would coincide with the multiple functions that we have already ascribed to the oxidizing substance.

We have seen that when the pancreas becomes functionally active its arterioles are caused to dilate by their vagal nerve terminals, and that the speed of the blood-flow through the organ is increased. Yet, while the net-work of capillaries is very rich, these *encircle* the secreting lobules, and, though in close relation with the glandular epithelium beneath the basement membrane, they in no way, as in the spleen, break up into reticulated tissue wherein their blood is poured; they merely lapse, as elsewhere in the organism, into venules, which ultimately carry the blood to the larger venous channels. Blood and trypsinogen do not come into contact, therefore, in the ducts of the typical pancreatic lobule: that which text-books employ to illustrate the origin, centripetal migration, and functional elimination of the zymogen granules. These are lost in the lobular lumina and ultimately reach the greater duct on its way to the intestine, without apparently having come into contact with the oxidizing substance.

But, this being the case, how can we account for the experimental evidence adduced by Schiff and Herzen and other physiologists who have confirmed their work? How can we explain, for instance, the digestion of 17 grammes of albumin in 7 hours with pancreas obtained from a normal cat and *no*

digestion in 12 hours with pancreas from one in which the vessels of the splenic hilum had been ligated: an experiment repeated many times, and always with identical results?

It is evident that, if—as believed by Schiff and Herzen—the circulatory cycle must be traversed by the splenic ferment before the pancreas can be influenced by it, this ferment will merely pass *through* the pancreas without in any way converting trypsinogen into trypsin, and fruitlessly re-enter the splenic venous current. There being no connection between blood-stream and trypsinogen and none between the latter and the splenic ferment, we are now reduced to either deny the need of any converting agency, and simultaneously close our eyes to all the experimental data adduced,—including Popelski's, which sustain the existence of *some* process which has imposed the necessity upon him of accounting for *results* witnessed,—or seek elsewhere for an explanation of the phenomena recorded. Thanks especially to the labors of Langerhans,[27] Laguesse,[28] and Opie,[29] this task will be greatly facilitated.

Laguesse having studied the islands of Langerhans in the pancreas of an adult man (an executed criminal) and of a child which has died several hours after birth without having taken nourishment, and in the sheep, reached the following deduction, quoted from one of our own reviews of his work.[30] "Long before the pancreas begins its function as a digestive gland granules of secretion accumulate in the internal zones of the cells; and, when these come *into contact with the blood,* a portion of them appear as though dissolved, while in others the granules are resorbed. It might be supposed, with some reservations, that an internal secretion always exists in the cell,—very much developed, however, and preceding the external secretion in the fœtus. Later, each cellular group would be first full, then acinous, furnishing alternately an internal and an external secretion." Opie refers to the observations of Kühne and Lea[31] in injected specimens, in which these in-

[27] Langerhans: Inaugural Dissertation, Berlin, 1869.
[28] Laguesse: Comptes-Rendus Hebdom. des séances et mémoires de la Société de biologie, Paris, No. 28, 1893.
[29] Opie: Johns Hopkins Hospital Bulletin, Sept., 1900.
[30] Laguesse: "Annual of the Universal Medical Sciences," vol. v, 1894.
[31] Kühne and Lea: Untersuch. a. d. Physiol. Inst. d. Univ. Heidelberg, ii, 488, 1882.

vestigators "found scattered through the organ glomerular structures composed of dilated and tortuous capillaries, and showed that these glomeruli correspond to the cell-groups which Langerhans described. The islands are penetrated by numerous wide, tortuous capillaries, which lie between cells, forming irregular, anastomosing columns. Material injected into the *duct* of the gland does not penetrate the islands." The view that the islands of Langerhans furnish an internal secretion is indirectly sustained, and the histological topography outlined seems to furnish a clue to the mechanism involved: *i.e., the existence of two sets of glands capable of yielding similar products, but adjusted individually, as regards distribution, to the needs of two systems: the digestive system and the circulatory system.*

To develop this proposition and that on page 379, we will employ the excellent paper of E. L. Opie,[32] in which the entire subject is not only reviewed, but also greatly elucidated through personal investigations. The quotations from his article will be limited, however, to the features bearing directly or indirectly upon the question in point, as given in the above italicized lines:—

"Schäfer and Diamare think that the vascular islets probably furnish an internal secretion. The only evidence in support of this suggestion is contained in the short preliminary notice of Ssobolew. He states that after feeding animals on carbohydrates the cells of the islands become more granular. After ligating the duct of Wirsung in dogs, the islands of Langerhans, he finds, are not involved in the sclerotic process which follows. He thinks that this fact explains the absence of glycosuria after ligation of the pancreatic ducts. In human cases I had observed after duct obstruction similar resistance of the islands to the consequent inflammation. In pancreases of two diabetics Ssobolew was unable to discover islands of Langerhans.

"In the human pancreas the islands were found to be more numerous in the splenic end, or tail, than elsewhere. To obtain a numerical statement of their relative abundance, their

[32] E. L. Opie: *Loc. cit.*

number was determined in a sectional area of 0.5 square centimeter. Sections about 10 millimeters thick were made from the enlarged duodenal portion of the pancreas, or the head; from the midportion, or body; and from the splenic end, or tail. The following table gives their number in an area of 0.5 square centimeter in sections taken from the head, body, and tail of ten normal organs:—

TABLE I.

	HEAD.	BODY.	TAIL.
I	14.0	13.0	30.0
II	39.0	25.0	42.0
III	4.0	4.0	19.0
IV	4.0	10.0	43.0
V	27.0	18.0	59.0
VI	25.0	27.0	26.0
VII	18.0	18.0	29.0
VIII	6.0	10.0	29.0
IX	44.0	32.0	61.0
X	14.0	23.0	32.0
Average	18.3	18.0	34.0

"The table shows that the islands are more abundant in the tail, or splenic end, than in the head and in the body, where they are present in approximately equal number. They are almost twice as numerous in sections from the tail as in those from other parts. Since the number in only one plane is recorded, in order to obtain their actual relative abundance it is necessary to square these figures. They are then found to be slightly less than three and a half times as numerous in the tail as elsewhere.

. . . . . .

"The cells composing the islands resemble those of the acini. They have a large, round, occasionally oval, vesicular nucleus and a conspicuous cell-body. The basal zone of the secreting cell, as is well known, stains deeply with nuclear dyes,—for example, hæmatoxylin or methylene blue,—while the central portion, which contains zymogen granules, remains unstained. The cells of the island, however, do not stain with nuclear dyes, while with eosin their protoplasm takes a homogeneous bright-pink color. The nuclei differ but little from

those of neighboring acini. They vary considerably in size, and not infrequently one finds very large, round, vesicular nuclei whose diameter is two or more times that of those about. Occasionally the cells, forming columns between which are the anastomosing capillaries, are very closely packed together, and nuclei are situated almost side by side; more frequently the cells of the island are less numerous and the nuclei are less closely crowded together.

"The outline of the island is usually round or oval, and is not infrequently accentuated by a delicate circle of fibrous tissue. In other instances the outline is less sharp, and the body accommodates its shape to that of the neighboring acini. Occasionally one sees, apparently within the island, 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. The impression is produced that the columns of the island are in continuity with cells having an acinar arrangement. Since the islands and the secreting acini have a common origin, it is not inconceivable that they may occasionally remain continuous in the adult organ. When the fœtal pancreas is affected by congenital syphilis, the islands, I have found, retain their continuity with the secreting structures.

"In the human pancreas the groups of acini about terminal ducts are not sharply defined by connective tissue; so that individual lobules, as in the human liver, are indistinctly marked off and in places apparently fuse with one another. In the pancreas of the cat the lobules, like those in the liver of the pig, are much more sharply outlined by interstitial tissue. Details of structure have been studied in the pancreas of the cat.

"The parenchyma is divided by septa of fibrous tissue into small polygonal areas in size and shape. When injected with Berlin blue, a small ramification of the ducts is found to penetrate the isolated group of acini. These subdivisions, or lobules, often appear completely isolated by fibrous tissue from those near by, but when one of them is traced through a series of sections its separation may be uniform, and in places one finds the parenchyma of adjacent lobules in contact, the

dividing septa being incomplete. That these polygonal structures are actually independent of one another and represent units of structure is readily demonstrated by causing an inflammatory increase of the interstitial tissue. If the pancreatic ducts of a cat are ligated and the animal killed at the end of two or three weeks, the gland is found to be the seat of a chronic interstitial inflammation, characterized by an increase of the interlobular tissue. The lobules are completely separated from one another by narrow bands of firm, fibrous tissue, and occur in sections as rounded, triangular, or polygonal areas of parenchyma.

"The islands of Langerhans occupy a position near the center of the lobule, and in the splenic end of the gland each lobule contains an island. In a given section many lobules whose limits are more or less distinctly outlined are seen to contain islands situated near their center, while in neighboring lobules such structures may not be discoverable. If, however, serial sections are studied, every lobule is found to contain an island. Its presence within the lobule is not constant in other parts of the organ, and in the extremity of the descending arm of the gland they are very few in number.

"The lobules are grouped about the medium-sized ducts. The main ducts give off branches approximately at right angles to their course. Branching one or more times, a duct forms the center of a group of lobules, which is usually elongated in form and tapers to a point at or near the surface of the gland. Such lobule groups are separated from one another by relatively wide bands of areolar tissue much looser in texture than that separating the individual lobules. The lobule groups in the fresh state or in tissue macerated a few days in Muller's fluid may be separated from one another by careful teasing. In the loose tissue lie the larger ducts, arteries, veins, and nerves. An artery and vein penetrate each lobule group in company with the duct, and ramify between its lobules. The smallest arteries occasionally penetrate the lobules, but usually branches, diminishing in size, give off capillaries which enter the lobule and form a close net-work between the gland-acini.

"The capillaries of the island of Langerhans form a