activity than later to the influence of remedies, especially organic preparations which actually nourish the nerve-cell and sustain its metabolism. The olfactory and gustatory apparatus thus develop more rapidly than in the older child, in whom the morbid process is more firmly established and therefore more resistant.

Important in this connection is the fact that where any or all the special senses show any marked degree of deficiency, the thymic nucleins should be supplemented by a preparation of phosphorus. Of special value in this connection is the official syrup of hypophosphites, which also contains a small dose of strychnine, $\frac{1}{12}$-grain to the drachm of syrup.

Cutaneous Sensibility.—The usual means to develop touch—smooth and rough surfaces, buttoning, warm and cold surfaces, etc., used for older children—are useless for infants. These require measures which excite the entire surface. In some mental defectives the temperature sense is so obtunded that a hot object, which normally causes rapid withdrawal of the hand in contact with it, fails even to attract their attention. And yet these same children, who will appear dull, sleepy and torpid in cold weather, will, during warm weather or under the influence of a mild febrile process, become unusually bright and active. Why is this? It is due, from my viewpoint, to a physical phenomenon the far-reaching importance of which I have long urged, viz., that *while ferments carry on metabolism in all tissues, the temperature to which these ferments are subjected in the tissue-cells governs the rate of metabolism in those cells.* Hence, warmth applied to the surface enhances metabolism and, therefore, the vital activities of the entire organism. We therefore have, in hot baths twice daily, or, in heliotherapy, exposing the nude body to solar heat during prolonged periods, as is now successfully done in the treatment of osseous and glandular tuberculosis, potent aids in the treatment of these cases. Indeed, by supplying the infant the glandular substances which carry on its vital functions and simultaneously heat to raise the activity of these functions to their highest potential, we antagonize precisely the slowness of metabolism in all tissues—including the cerebrospinal system—to which the hereditary forms of idiocy and mental backness are due.

CHAPTER VII.

THE ADRENAL SECRETION AND FUNCTIONAL ACTIVITY.

In the preceding six editions I described (1) the process through which the adrenal secretion (converted in the lungs into adrenoxidase, the oxidizing constituent of the hemoglobin) carried on, from my viewpoint, its functions in various organs, and (2) the manner in which the nervous system governed its distribution. Briefly, I submitted the view that in the skeletal muscles and the lachrymal, salivary, sweat and mammary glands as examples of other organs, the adrenoxidase was the physico-chemical agent through which cellular metabolism was sustained by oxidation, and that there were two phases to this process: the *passive,* during which the organ was inactive owing to the reduced quantity of adrenoxidase supplied to the tissue-cells by the artificial blood; and the *active,* during which a more or less great increase of adrenoxidase reached these cells in a correspondingly greater volume of arterial blood, initiated and sustained functional activity in that same organ.

As to the manner in which the distribution of adrenoxidase was carried on, I submitted the evidence which had led to the conclusion that two kinds of nerves took part in the process: 1, motor or secreto-motor fibers supplied by one of the cranial nerves (the pneumogastric, facial, etc.), the terminals of which caused the arterioles to the organs to dilate and to admit an excess of the oxidizing substance of the blood, adrenoxidase, into their cellular elements, thus initiating active function, *e.g.,* contraction, secretion, etc; 2, constrictor fibers, supplied by the sympathetic, which caused the previously dilated arterioles to contract, when this active function was to cease, thus diminishing the supply of adrenoxidase to the organ. This subject being considered at length in the second volume with explanatory illustrations, the reader is referred to that volume, pages 1115 and 1185.

The same method of nervous control was shown to prevail in the stomach—digestion being initiated by dilation of its arterioles through the pneumogastric and arrested by the sympathetic—and also in the intestines. These organs were shown, however, to initiate a defensive process against toxic proteins, bacteria and their toxins, etc., by means of their secretions and also through phagocytes supplied by the agminated follicles. The cæcum was included in this defensive mechanism, the vermiform appendix aiding it by supplying phagocytes and a secretion rich in bactericidal and antitoxic antibodies. This whole subject is also considered in the second volume (fourteenth chapter), to which the reader is referred.

The same features will now be considered in their relation with the liver, pancreas, spleen, cardiovascular and pulmonary systems and the kidneys.

THE LIVER AND ITS PHYSICO-CHEMICAL FUNCTIONS.

Considerable evidence is available to show that oxidation is one of the most active factors of hepatic functions, and yet it must be admitted that, according to prevailing views, there is no blood-supply capable of accounting for this powerful source of energy. To the portal vein, essentially a channel for physiologically impotent blood,—*i.e.*, blood replete with the waste-products of four important organs and the oxygen of which has been utilized in these organs,—is ascribed this preponderating rôle. On the other hand, the hepatic artery is thought to supply the liver "with the blood of nutrition." Textbooks on physiology, therefore, seldom refer to this vessel; works on histology hardly grant it more than two or three lines, if they refer to it at all. In textbooks on anatomy it receives more attention, but only in its general topographical bearing.

As viewed from my standpoint, *the hepatic artery does not only supply the liver with its nutritional blood, but simultaneously with the blood upon which all its functions depend.*

To develop this proposition a review of the histology of the lobule is necessary. Clarkson[1] gives the following complete, though succinct, description of this wonderful little body

[1] Clarkson: "Textbook of Histology," 1896.

—about one-twentieth of an inch in diameter—and which in itself has been termed a "miniature liver":—

"A lobule of the liver is polygonal in shape, and is composed chiefly of a number of gland-tubes, which radiate from near the center of the lobule to the periphery, where they open into their ducts. Thus, the blind terminal end of the tube is turned toward the center of the lobule; the ducts at the periphery lie in the interlobular connective tissue, which to the naked eye marks the boundaries of the lobule.

"The blood brought to the liver by the *portal vein*[2] is conveyed along its subdividing branches till the ultimate subdivisions are reached, which lie, together with the bile, in the connective tissue surrounding the lobules. Here capillaries are given off which pierce the lobule and pass between the radiating gland-tubes to reach the center, where they open into the intralobular radicle of the efferent vein of the liver, the *hepatic vein*. These small hepatic radicles open into the larger vessel, —the *sublobular vein*,—and the sublobular veins unite to contribute to the hepatic vein itself. The walls of the branches of the hepatic vein are destitute of muscular fibers and the adventitia is extremely thin. The radiating gland-tubes anastomose laterally with each other, as do the capillaries also. The meshes of the net-works are elongated in a radical direction. Thus, a lobule is composed of a radiating system of gland-tubes and a corresponding radiating system of capillaries lying between them. A very minute quantity of connective tissue accompanies the capillaries as an adventitia and in this lymphatic channels are to be found separating the gland-tubule from the blood-vessel.

"The lobule is surrounded (in part or whole) with connective tissue supporting branches of the afferent portal vein, —the feeder of the capillary net-work,—and the *bile-ducts*, which receive the secretion of the gland-tubules. Thus, the blood flows from the periphery to the center of the lobule; the bile, from the center to the periphery.

"But in addition to the afferent portal vein and the bile-ducts another vessel is found in the interlobular connective

[2] The italics are my own.

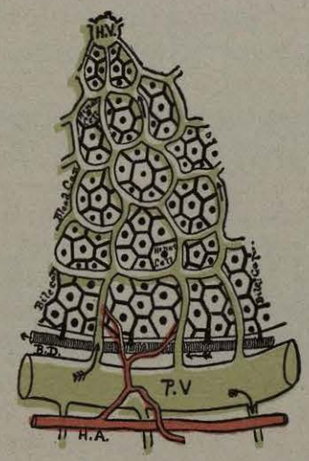
tissue. This is the *hepatic artery,* which supplies blood for the nutrition of the connective tissue of the organ, the vessel-walls, etc. It ultimately terminates in the small portal veins, and perhaps partly in the capillaries in the periphery of the lobules."

There exists some uncertainty as to the manner in which the subdivisions of the hepatic artery are related to the other perilobular and intralobular vessels. Pick and Howden[3] refer to its terminal distribution as follows: "Finally, it gives off interlobular branches, which form a plexus on the outer side of each lobule, to supply its wall and the accompanying bile-ducts. From this lobular branches *enter the lobule* and end in the capillary net-work between the cells. Some anatomists, however, doubt whether it transmits any blood directly to the capillary net-work." Harrison Allen[4] says: "Each lobule is a miniature liver having at its periphery between the lobules branches of the portal vein and hepatic artery (interlobular branches) which freely *intercommunicate* and form *through the lobule,* between its periphery and center, a capillary net-work. Directly at the center the venules of this net-work (intralobular vessels) converge to form radicles of the hepatic vein." Labadie-Lagrave[5] states that, "as regards the divisions (of the hepatic artery) destined for the lobules, they penetrate conjointly with interlobular veins, *but without communicating* with them, in the interior of the lobule, in the form of capillaries distributed to the *central vein.*" In the presence of these divergent views, which but exemplify those of other authors, our only choice lies in the selection of the one region which all authors seem to consider as reached by the artery: *i.e.,* the periphery of the lobule. But, as all concede, also, that the arterial capillaries penetrate in one way or another to the intralobular supply, we will adopt—though we believe that Harrison Allen's definition is the true one—the more conservative distribution indicated in the annexed engraving by Piersol, who, in accord with many histologists, describes the

[3] Pick and Howden: "Gray's Anatomy"; edition, 1901.
[4] Harrison Allen: "Human Anatomy," 1884.
[5] Labadie-Lagrave: "Traité des Maladies du Foie," 1892.

hepatic artery as "supplying nutrition to the interlobular structures and terminating in the lobular capillary net-work."

A noteworthy feature of the capillary net-work enveloping the cellular bodies is that each mesh does not merely cover one cell, but several. Indeed, were it otherwise, the bile-capillaries could not exist as individual channels and give an uninterrupted free way to their contents without allowing the bile to penetrate the blood-stream. To prevent this, and yet simultaneously insure perfect exposure to the blood and lymph, a very simple arrangement exists: *i.e.,* three or more of the



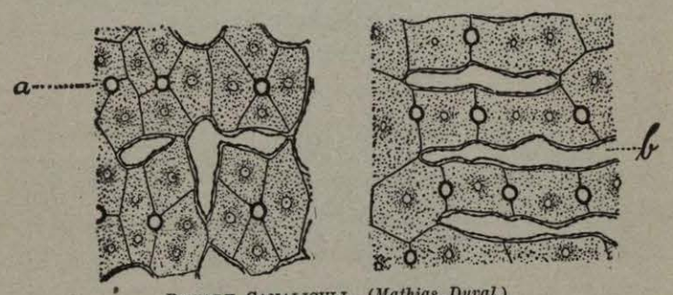
SECTION OF LIVER SHOWING THE LOBULES, CELLS, AND THE BLOOD-SUPPLY. (*Piersol.*)

P.V., Portal vein. H.A., Hepatic artery. H.V., Hepatic vein.

cells (usually polyhedral) are joined longitudinally, and, while the narrow passage in the center of the group thus formed serves as a bile-channel, the outside only is in contact with the blood- and lymph- capillaries. When only two cells are thus joined, the surfaces in contact have in their center a small opening, which, being adjusted to that of the adjoining cell, insures the continuity of the channel. It thus becomes clear that the blood-plasma may penetrate the cell, undergo or induce metabolism therein, and the product pass out through the intercellular biliary passages or bile-capillaries. The cells

are so joined as to form continuous, though correlated, channels, which radiate from the center of the lobule to its periphery, where they join the interlobular bile-channels.

The intimate structure of the hepatic cell is peculiar. It possesses no limiting membrane; but its peripheral protoplasm is more dense than that of its other parts and the pseudocovering so formed serves as the outer wall for numerous cavities or vacuoles which inosculate irregularly throughout its interior. All these vacuoles, however, more or less directly converge toward the center, where they meet a protoplasmic mass, which in turn contains one and sometimes two nuclei. The cell, apart from its nucleus, suggests a miniature sponge the cavities of which (secretion vacuoles) become filled with



BILIARY CANALICULI. (*Mathias Duval.*)

a, A biliary canaliculus cut transversely. *b*, Intercellular capillary.

glycogen. This substance seems to accumulate in the *outer* vacuoles, which appear wider in this location than the inner ones, when, by artificial means, the glycogen has been removed. It is perhaps noteworthy that this substance accumulates in the part of the cell nearest the blood-vessels and that the droplets, or "granules," considered as bile are most abundant in the opposite direction: *i.e.*, near the bile-capillaries. These "droplets" accumulate between periods of digestion and diminish during this process. A delicate canaliculus connects this part of the cell with the biliary channel. The vacuoles in the paraplasm, according to Kupffer, "play an important part in the secretion of the cell, and are due to the confluence of minute drops of bile into a large globule. As soon as the vacuole has attained a certain size it tends to empty its contents into the bile-capillary through a small tubule connecting the vacuole with the bile-capillary." Kupffer's main vacuole is thought by him to constitute an intracellular vesicle connected with the bile-capillaries by means of delicate tubes.

The nerves of the liver enter the organ at the transverse fissure and accompany the blood-vessels and lymph-vessels to the interlobular spaces. That the vagus causes vasodilation of the hepatic arterioles was first observed by Cavazzani and Manca.[6] François-Franck and Hallion[7] also witnessed vasodilator effects on stimulating the central segment of the divided vagus with a weak current. Bruno[8] has shown, moreover, that the flow of bile was increased concomitantly with the passage of food-products through the pylorus under the influence of the vagus.

The vasoconstrictor action of the sympathetic nerve on the liver was pointed out by Vulpian,[9] who found that stimulation of nerves derived from the cœliac plexus caused anæmia of the hepatic area to which they were distributed. Haffter, Samuel and Frerichs all observed congestive coloration phenomena on dividing the splanchnic nerve and the cœliac plexus, similar to those that follow, in the ear, face, etc., section of the sympathetic nerve in the neck. Mall[10] showed that the splanchnics also contained vasomotor fibers for the portal vein. Bayliss and Starling[11] then found a rise of the blood-pressure in the portal vein occurred in the dog, when the thoracic nerves between the third and eleventh thoracic inclusive were stimulated, the maximum effect following excitation of the fifth to the ninth inclusive. Cavazzani and Manca[12] were led to conclude that hepatic vessels were also under the influence of such nerves by passing warm saline solution at a given pressure through these vessels and measuring the outflow in a given time. This was confirmed by François-Franck and Hallion.[13] The latter physiologists showed, moreover, that the

[6] Cavazzani and Manca: Archives ital. de biol., T. xxiv, p. 33, 1895.
[7] François-Franck and Hallion: Arch. de physiol. norm. et path., T. viii and ix, 1896.
[8] Bruno: Archives des Sc. biol., T. vii, p. 87, 1899.
[9] Vulpian: C.-r. de la Soc. de biol., p. 5, 1858.
[10] Mall: Archiv f. Physiol., S. 409, 1892.
[11] Bayliss and Starling: Jour. of Physiol., vol. xvii, p. 120, 1894.
[12] Cavazzani and Manca: *Loc. cit.*
[13] François-Franck and Hallion: *Loc. cit.*

true vasoconstrictor effects of the sympathetic were produced by fibers derived from the cord on a level with the sixth thoracic and second lumbar inclusive, all passing to the splanchnic nerves.

On the whole, it is evident that *the functions of the liver are incited through vagal vasodilators and inhibited by sympathetic vasoconstrictors as in the stomach and intestines.*

Our inquiry into the character and composition of the substances that are transformed in the liver and of the secretions of this organ must necessarily include the blood of the portal vein, since it contains whatever products of metabolism the organ is thought to transform. We shall, therefore, begin with this channel, which brings to the liver essentially venous blood, since it contains that utilized by four organs — the stomach and the intestines, the pancreas and the spleen—in which the metabolic products include, besides those incident upon tissue-waste, food metabolites, physiological toxics, etc.

As is well known, there exist in the liver's secretions distinct evidences of association with splenic hæmatopoietic or hæmolytic functions. The liver is known to modify the composition of the blood as it passes through it, but the purposes of the alterations involved are not established.

The Splenic Vein.—The path from the spleen to the portal vein, through the splenic vein, is a direct one, and the blood the spleen sends to the liver is not, therefore, modified in transit by any other organ, though the splenic *vein* receives a few branches from the pancreas and stomach. Still, these are mere tributaries to a common channel, and, as the arterial supply comes directly from the cœliac plexus, we can say that the spleen receives nothing but pure, freshly-oxygenated blood in great quantities. Indeed, the splenic artery is remarkably large for the dimensions of the organ, and *we can easily account for the so-called "ague-cake" and the temporary enlargement that occurs during malarial and other fevers when we include suprarenal overactivity and excessive vascular tension in the pathogenesis of these phenomena.*

To this we cannot ascribe, however, the post-prandial splenic enlargement, which attains its maximum about five hours after an ordinary meal, since we now know how independently of suprarenal overactivity and merely through nervous influence an organ's function can be excited and governed; indeed, sympathetic and pneumogastric again unite here to account for a *passive* period and for an *active* period: that of gradual enlargement. "The turgescence of the spleen seems to be due to a relaxation both of the arteries and of the muscular tissue of the capsule and of the trabeculæ" says Professor Foster: evidence that we are again dealing with dilation of the arterioles to increase the influx of blood into the functional areas,—the physiological process we have found in other organs.

That the organ is concerned with some process incident upon blood-changes is evident. But what is this process? The various points that may afford a clue are these: red blood-corpuscles have been found in various stages of disorganization in the organ, but in the interior of amœboid cells buried in the pulp. The spleen-pulp also contains an albuminoid proteid rich in iron, and a pigment which shows considerable carbon. That an active combustion process may go on in the organ is suggested not only by the latter, but also by the presence of various purin bases; xanthin, hypoxanthin, and their end-product, uric acid. Various other acids—acetic, butyric, formic, succinic, lactic, etc. — are also found in relatively large quantities. This appears suggestive when we consider the large quantity of oxidizing substance that must course through the organ especially during post-prandial activity.

The spleen also seems to be a leucocytogenic center, since the splenic vein contains a much larger proportion of leucocytes than the splenic artery. But as these leucocytes leave the organ through the splenic vein, and ultimately, therefore, reach the liver through the portal, they must either be connected with some function in the liver or be destroyed there. Again, the arterial blood has been found to lose one-half of its red corpuscles; at least, blood from the spleen contains one-half of those found in the blood of the splenic arteries. Coupled with the finding of disorganized remnants of these bodies in the splenic pulp, this certainly suggests, as is generally believed, that red blood-disks are disintegrated and white corpuscles created in the spleen. Indeed, the portal blood is poor in red disks. Yet, the hepatic vein is still poorer in them

in the sense that the proportion of red to white cells is as four in the subhepatic vein is to one in the portal vein, after the blood has been submitted to the effects of hepatic functions. It seems clear, therefore, that red corpuscles are destroyed both in the spleen and in the liver, and that, since the spleen is possessed of no external duct, it is in the liver's secretions that we should find proofs of this dissociation of corpuscular elements. Indeed, we have in bilirubin, a bile-pigment derived from hæmoglobin, direct evidence of this fact.

The Hepatic Blood-pigments.—We have already analyzed (in the second chapter) the process through which various blood-pigments are transformed one into another. We will now only refer, therefore, to the relations between these bodies and the spleno-hepatic functions.

We ascertained that the changes undergone in the liver represented but a portion of a cycle of which the intestines were the starting-point, bilirubin (excepting that transformed into urobilin and stercorin) being reabsorbed from the intestine and again used in the building up of hæmoglobin. Experimental evidence was adduced to show (Macallum) that in an animal fed on albuminate of iron free leucocytes crowded with iron-pigment could be traced in transit through the intestinal mucous membrane in the villi, and that similar leucocytes had been found in the spleen and in the liver. But can we conclude from this that the iron-laden leucocytes find their way to the spleen and that this organ constitutes a part of the cycle? The anatomical relations of the structures involved show that, even if such an arrangement did exist, it could serve no useful purpose, since the leucocytes would but penetrate the splenic structures to again enter the portal circulation. Obviously, the only pathway available anatomically is the venous one, since Macallum found the "leucocytes crowded with granules of iron-pigments" in the *venules* of the villi.

The single venous channel at our disposal, therefore, is that of the distribution of the villi, the ileum and jejunum mainly, *i.e.*, the superior mesenteric veins,—which again lead us to the portal vein. This probably means that the iron thus taken from the intestine is not ready for the circulation, and

that it must undergo a secondary process in the liver before it can serve its physiological purpose in the arterial circulation. This is sustained by the prevailing view as to the functions of the spleen, *i.e.*, that it disintegrates worn-out red corpuscles, and also by the great increase of leucocytes observed in the splenic vein as compared to the proportion of these cells in the artery. It seems logical, therefore, to conclude that *both in the lymphatic structures of the intestine and in those of the spleen leucocytes are formed which carry iron-pigments to the portal vein; those from the intestine reach the latter by the superior mesenteric vein, and those from the spleen by the splenic vein.* As Macallum observed iron-pigment leucocytes in the spleen similar to those witnessed in the intestinal villi, and the venules of the latter and the splenic vein ultimately transmitting their blood to the portal vein, no other conclusion seems possible.

The similarity of the general mechanism involved suggests the presence of correlated functions. Thus, *in the spleen the leucocytes are formed in situ, pass out into the pulp-channels, and take up the iron-pigment and carry it out to the liver; in the intestine they are formed in a similar structure,—the follicle,—pass out into the intestinal channel, take on a similar supply of blood-pigment, re-enter through the villi into the venous system, and also proceed to the liver.* True, I have previously ascribed bactericidal properties to the leucocytes produced by the intestinal follicles; but the chemotactic property of the leucocytes, the existence of which is shown by their ability to take up the pigments, serves but to demonstrate that they must also be endowed at least with phagocytic attributes.

It was also shown, in the earlier editions of this work, that, while the adrenals supply an oxidizing substance to the blood, insufficiency of the adrenals leads to the formation of a compound inferior to hæmoglobin in oxygen-absorbing powers,—*i.e.*, methæmoglobin; and, furthermore, that hæmatoporphyrin is formed when the suprarenal insufficiency is still further advanced, hæmoglobin being unable to hold itself together, as it were, and to absorb oxygen. Again, we saw that hæmoglobin is reduced to hæmatin when the reaction with the reducing agent occurs in the *presence* of oxygen. In the *absence* of oxygen