would thus paralyze them or cause what Arnaud has termed "suprarenal apoplexy": *i.e.*, intrinsic hæmorrhage. To ascertain whether such a nervous influence can exist, and, if it does, whether a poison can stimulate the glands through the latter's nerve-supply, is necessary before further progress can be made.

Biedl[67] studied the effects of various poisons, particularly atropine, to ascertain whether they influenced the character or quantity of suprarenal secretion, and obtained negative results. But can this be said to apply to *all* poisons? A close analysis of this physiologist's work has led me to interpret his experiments in a manner that is not in accord with his conclusion. He states that he found blood-pressure to be increased in the organ by the interruption of artificial respiration. This interruption appears to me to point to an accumulation in the organism of *products of metabolism,* and therefore of poisons of a class which stand out prominently as the basis of phenomena that promptly end in death. That products of metabolism may with justice be considered as toxic is shown by a detail in Langlois's work, the importance of which does not seem to have attracted sufficient attention: While decapsulated frogs died in 48 hours during summer months, they lived 12 days in the winter, *i.e.*, during hibernation, when metabolic processes are at their lowest ebb. It required a certain ratio of toxic elements to the body-weight to bring on the culminating phenomena; the "fatal dose" was made up in 48 hours, in summer,—*i.e.*, when the full activity and proportionate catabolism prevailed; the same relative dose could only be made up in six times 48 hours when hibernal lethargy reduced tissue-waste in proportion. Thus, Biedl's experiments are not negative in this direction, as he deemed them to be. They appear to me to suggest that, as will be shown in these pages, all toxics do not influence the adrenals with equally marked activity.

Biedl also found that, when the splanchnic nerve was cut and the suprarenal branches were stimulated, hyperæmia appeared in the organs. Howell refers to the striking evidence afforded by the effects of electrical stimulation. If, after cutting the splanchnic nerve and introducing a cannula into the suprarenal vein, the blood is collected and the peripheral end

[67] Biedl: Pflüger's Archiv, vol. lxvii, H. 9 and 10, 1897.

of the cut nerve is stimulated, the quantity of blood obtained in a definite time is not increased, but it is found to contain more of the blood-pressure-raising substance: a fact which indicates that its secretory activity is increased. He therefore concludes that the adrenals act as true glands, and that they are provided with a reflex mechanism corresponding to that of the latter. Biedl also expressed his conviction that secretory fibers as well as vasodilator fibers are present in the splanchnic nerves. Dogiel[68] likewise found that the medullary nerves form complicated plexiform arrangements which terminate upon the surface of the glandular elements, and, furthermore, that the nerve-cells in no way differ from those of any sympathetic ganglion.

This experiment tends to show, and additional labors have only served to emphasize their soundness, that the functions of the adrenals are governed by the splanchnic nerve. We are thus brought to conclude that, in keeping with many important functions, those of the adrenals are regulated by some center (which I will describe farther on) somewhere in the cerebro-spinal axis. Again, we learn that stimulation of this nerve increases the functional activity of the adrenals *without* increasing the volume of blood given out by the gland *with* the secretion. But as shown by Claude Bernard, it is by augumenting the blood supplied to a gland that its functions are enhanced; and it happens also that it is not in the secreting elements that the hæmorrhages into the adrenals occur, but mainly in the cortical zone. This indicates that the blood-streams which serve to increase the secretory activity organs do not yield their blood through the vessels which transfer the adrenal secretion to the inferior vena cava. We have such vessels—which, unlike the veins to the latter, carry venous blood—in the many veins which the adrenals send to the renal veins.

The bulk of evidence, therefore, tends to show that *increased functional activity of the adrenals being attended by an increased supply of blood to these organs, it must be considered among the predisposing causes of adrenal hæmorrhage.*

But we have seen also that the splanchnic contains the secretory nerves to the adrenals, and that this implicates the

[68] Dogiel: Archiv f. Anatomie und Physiologie, p. 90, 1894.

existence of some governing center for these organs. When we add to this the antitoxic properties of the adrenal secretion, it appears possible at least that *it is partly by exciting the adrenal center that various poisons predispose the adrenals to hæmorrhage,* the purpose being, as we shall see, to augment the antitoxic power of the blood.

Passive Congestion of the Adrenals by Toxics which Depress the Blood-pressure.—Oliver and Schäfer, by plethysmographic observations upon the limbs and spleen, found that injections of suprarenal extract produced great vascular constriction, chiefly in the splanchnic area. That deficiency of suprarenal secretion in the organism should produce the opposite result in the same region is shown by the fact that removal of the adrenals is followed by relaxation of the same great vascular channels.

This central engorgement of suprarenal origin—greatly accentuated through the fact that "vessels supplied with a muscular coat and capillaries are antagonistic in contraction and dilation"—seems far reaching in its application. The symptoms of acute arsenic poisoning will serve to illustrate this fact.

As a result of the central accumulation of blood, the extremities and peripheral tissues, more or less depleted of theirs, are cold; the muscles, also deprived of the greater part of their blood, lose their power; the tension upon the abdominal vessels and neighboring structures, including the unusually rich nervous net-works, produces the intense abdominal pain; engorgement of the intestinal vessels gives rise to copious diarrhœa, which by causing reduction of liquids tends to reduce the renal secretion and sometimes to cause anuria. The depletion of the cerebral vessels accounts for the syncope, and the auto-intoxication, through accumulation of waste-products, for the convulsions. These phenomena recall so clearly the symptoms that follow removal of the adrenals that we cannot but suspect that arsenic must in some way arrest the functions of these organs.

Still, while the various morbid conditions outlined account for the symptoms recorded, closer investigation soon shows that they are only satisfactory as far as they go, and that some features of the symptom-complex are not fully met. Thus,

general relaxation of the vascular system means sudden increase of caliber of all vessels, and, therefore, a corresponding increase of area for the blood. Why should it, under these circumstances, accumulate in the larger trunks? Why should it not merely lie dormant in the relaxed vessels evenly distributed throughout them all? Again, gravitation prevails in our body precisely as it does elsewhere. Why should the blood not fill the vessels of the lowest levels of the organism and the back, the nates, the calves, and the heels of the recumbent patient become hypostatically congested, red, and hot, while his toes, knees, abdomen, and face, blanched and cold, reveal by their pallor and coldness the total absence of blood, which has gone to find its level? Instead of this the *entire* surface is frigid and blanched; the lowest portions of the body as well as the uppermost show that all the peripheral capillaries are depleted and collapsed, the blood in them having been drawn internally: *i.e.,* toward the great abdominal trunks. Again, the intensity of the pain seems to indicate not mere engorgement, but inordinate, disruptive, centrifugal pressure, for which mere relaxation of the vascular walls cannot account.

On the whole, we are forced to conclude that there must be an overpowering display of centripetal flux from the peripheral capillaries, arterial and venous, as soon as the vasoconstrictor mechanism fails to hold the central vascular walls up to their normal tone. That it is mechanical is suggested by its mode; that it enters into the domain of hydrokinetics is evident; and that loss of the normal equipoise between two forces forms the basis of the process affirms itself on all sides. The solution of the problem suggests itself when we recall, besides the fact that the total sectional area of the capillaries is seven hundred times that of the aorta, the manner in which the capillaries are affected when muscular vessels are dilated. The blood in them, as we have seen, is compressed by the resiliency of their walls and other tissue surrounding them, and literally floods the abdominal organs. Indeed, *the peripheral system contains as many sources of pressure as there are capillary tubes in it*—enough many times to account for all the mooted points just reviewed.

To illustrate the violence of the power exerted in this con-

nection, I may refer to the principle of hydrokinetics,—Pascal's principle,—which underlies the whole mechanical process. This physicist completely filled a strong cask with water, closed it hermetically, then inserted the end of a long, narrow, and close-fitting glass tube through a hole in one of the staves. Into the upper end of the tube, which stood upright, he then slowly poured water. Long before the tube had been filled the cask burst, owing to the excessive pressure within its walls. How was this pressure exercised? "The pressure of a fluid being due to its weight," the pressure in the upper layers of the water in the tube was slight, while that in its lower layers had increased in proportion with its distance from the top, since "pressure at any point in a liquid varies as its depth." "A pressure exerted on a fluid inclosed in a receptacle" being "transmitted undiminished to every part of that receptacle, and the total pressure exerted on the interior of the latter" being "equal to the area multiplied by the pressure per unit of area," a centrifugal display of force occurred—which far surpassed the resistance of the cask, and it had to yield. The hydraulic press, by means of which the hand of a child can break a steel rail, is based upon this principle.

These principles prevail in the human organism precisely as they do elsewhere in Nature. In the large vascular trunks of the abdomen, abdominal and thoracic viscera, etc., we have closed channels typifying the cask; in the narrow muscular vessels leading to them we have a multitude of conduits portraying the glass tube. Finally, we have the aggregate of pressure of millions of contractile, resilient capillary vessels containing a mass of blood (so great in comparison to the larger vascular structures that these have been considered as subsidiaries to the capillary system) to represent the gobletful of water with which Pascal indirectly caused explosion of his cask. That we have ample power to account for the symptoms mentioned is evident. It also accounts for suprarenal hæmorrhage when violent toxæmia is present. The rich vascular supply of the organs is well shown in the annexed colored plate prepared by J. M. Flint in the course of an exhaustive study of their anatomy, and published in the Johns Hopkins Hospital Reports.

Obviously the application of this principle is subject to limitations which the volume of blood accumulated in the vessels of the trunk impose. Admitting, for purposes of illustration, that all the blood of the organism has been forced into the interior of the body, its mass represents a fixed area which the various internal structures must furnish. Thus, while the large vascular trunks bear the brunt of the pressure, all the neighboring organs, including their capillaries, become engorged in proportion as the quantity of blood added to their normal contents is great. In other words, the blood accommodates itself to any room it can find after the larger vascular trunks are engorged, whether it be in a blood-vessel or a viscus. Thus, Boinet, in 45 of his 59 decapsulated rats, found hæmorrhage in the lungs in 16, in the spleen in 41, in the thyroid in 13, in the thymus in 11, in the kidneys in 8, in the liver in 5, and in the spinal cord in 5.

All this further emphasizes the practical bearing of the postulate: "Vessels supplied with a muscular coat and capillaries are antagonistic in contraction and dilation." It illustrates, furthermore, the importance of remembering that those toxins and other poisons which cause accumulation of blood in the splanchnic area also cause passive congestion of the *adrenal vessels* owing to the proximity of these channels and their direct relations with this area. This would occur for example with curarine, of which Tillie[69] writes: "With larger doses *there is dilation of the abdominal vessels* and hence accumulation of blood, little or nothing of this fluid entering the empty ventricle, notwithstanding that the heart may continue to beat.

When, therefore, we are dealing with infections such as Asiatic cholera, true cholera infantum, the anæmias, and other disorders in which extreme pallor prevails; or in acute intoxication by arsenic, chloral, alcohol, ptomaines, the coal-tar autopyretics and other agents which also provoke cutaneous pallor, there is good ground for the belief that, in addition to the recession of blood to the deep channels of the splanchnic area, and into the viscera, *including the adrenals,* we should take into account Pascal's hydrokinetic principle. Indeed, we are not dealing here with a single stream, as in the experiment referred

[69] Tillie: Medical Chronicle, March, 1891.

to, but with a multitude of streams derived from all the peripheral capillaries of the body. Moreover, we have, as an additional factor tending further to project the blood inwardly, the resiliency of the peripheral arterioles when the blood-stream passing through them is insufficient to cause them to retain their normal relative caliber.

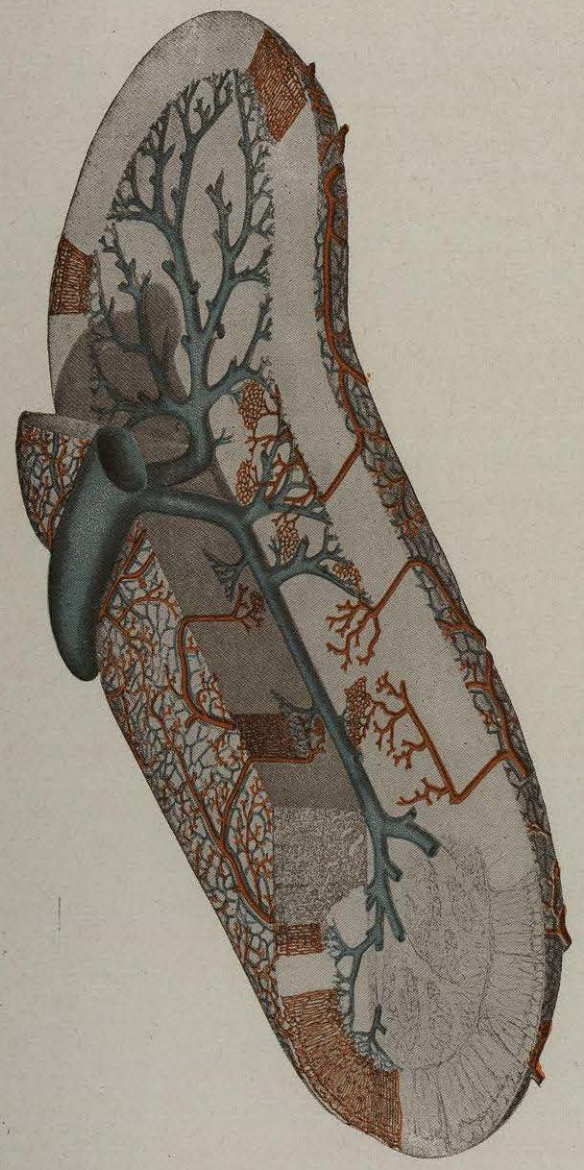
All these mechanical factors added to the passive hyperæmia incident upon the accumulation of blood in the splanchnic area seem clearly to expose the adrenals to a degree of centrifugal pressure at least equal to that produced by marked elevation of the general blood-pressure. It seems permissible to conclude, therefore, (1) *that the adrenals may become passively congested by the accumulation of blood in the splanchnic area and the abdominal viscera, caused by toxins and other poisons and drugs which markedly lower the blood-pressure, and* (2) *that the disruptive power of this adrenal congestion is enhanced by the centripetal pressure of the peripheral blood (Pascal's principle) and also by the pressure due to the resiliency of the peripheral blood-vessels.*

The heart, lungs and brain being correspondingly despoiled of blood, their functions are inhibited in proportion.

Degenerative Effects of Toxins and other Poisons on the Adrenals.—This is another factor which must be taken into account, especially where toxins are concerned. They show a wide range of selective power, and, in keeping with all sufficiently active poisons, are capable of irritating tissue cells and of causing necrosis and degeneration.

Before studying the manner in which the adrenals react under the influence of these poisons, it may be well to illustrate the primary steps of the process in accord with previously submitted conclusions, viz., the hyperæmia and the absence of pathogenic organisms in the glands proper. René Wybauw, for example,[70] injected diphtheria toxin into the peritoneal cavity of a large number of guinea-pigs, causing death within three days. In all these animals the adrenals had become somewhat enlarged and showed intense hyperæmia, the central vein being particularly engorged. In one of the animals the disease fol-

[70] René Wybauw: Annales de la Société Royale des Sciences Méd. et Nat. de Bruxelles, vol. vi, p. 134, Nos. 2 and 3, 1897.



CIRCULATION OF THE ADRENALS IN THE DOG. *[J. M. Flint.]*

[Johns Hopkins Hospital Reports.]

lowed an acute course; the vascular structures had yielded to the pressure and the organs showed abundant hæmorrhages. The reticular and medullary zones, in which capillaries are especially abundant, presented the most marked lesions.

We have already seen that Abelous and Langlois also found that the injection of various bacterial cultures caused vascular lesions varying from slight congestion to severe hæmorrhage. Two cases, also referred to previously, are particularly interesting in this connection: In the one, a case of acute toxæmia reported by Andrewes,[71] death occurred in 36 hours, and the adrenals alone showed lesions—interstitial hæmorrhage. In the other, reported by W. S. Colman,[72] the symptoms also indicated a general infection; death occurred in about 25 hours, and no lesion other than suprarenal interstitial hæmorrhage was found. The interesting feature of these cases, however, is that both observers submitted blood taken from the hæmorrhagic foci in the organs to bacteriological examination. Andrewes invariably obtained sterile cultures, and he states that, if any organisms were present, "there were none that grew upon ordinary media or stained with ordinary reagents." Colman not only reached the same result with blood from the adrenals proper, but with blood taken from other organs. The cases had doubtless been caused by a specific toxin, but with the ever-present hyperæmia as the only morbid feature.

But this is evidently but a stage of the morbid process, succeeded by local lesions. Wybauw[73] states that he has invariably found in these organs, after the injection of diphtheric toxins in rabbits, the histological lesions found elsewhere in this disease.

He further noted that the point of union of the reticular and medullary zones, where the capillaries are especially numerous, presented the well-known type of degeneration, while the slides also clearly showed all the stages of cellular destruction, with more or less disintegration of the nuclei. The latter were also undergoing retrogressive stages, gradual loss of regular outline, irregular perimetric retraction, etc. He likewise

[71] Andrewes: Lancet, May 7, 1898.
[72] W. S. Colman: Lancet, May 7, 1898.
[73] Wybauw: *Loc. cit.*, pp. 134 and 165.

examined microscopically the adrenals of a guinea-pig killed with cholera germs, but in this connection he says: "The adrenals are the seat of much less pronounced changes than those of the diphtheric guinea-pig. They are redder than normal. But the examination shows lesions which must certainly be produced by the same mechanism. The cells are irregular, the nucleus having lost in places its characteristic structure," etc. In a case of broncho-pneumonia following tracheotomy for diphtheria, he was able to note the same changes that he had observed in the diphtheric rabbits and choleraic guinea-pigs, but less marked, the patient having died of the concomitant disease before the diphtheric process had become far advanced.

Arnaud,[74] in a case of suprarenal hæmorrhage associated with liver-abscess, also found lesions in the suprarenal medulla characterized by cellular degeneration, granular disintegration, etc.: *i.e.*, a general necrobiosis of septic origin. If to these results we add those of Andrews and Colman, referred to above, it would seem permissible to conclude with Wybauw, that bacterial toxins possess a direct irritative action upon adrenal tissue.

But this observer ascribes to the adrenals a special sensitiveness to the influence of diphtheric toxins. While this may be true, it is more likely that, inasmuch as a specific toxin does not produce a characteristic lesion in them, the phenomena witnessed, histological and symptomatic, should rather be considered as expressions of excessive stimulation or exhaustion of these organs common to all toxins. The various toxins differ in potency precisely as do other poisons; it is also self-evident that various poisons must affect the adrenals in proportion as their virulence and dose are great.

The common action of various toxins is suggested by other facts. Thus, Langlois and Charrin[75] invariably noted hypertrophy of the suprarenal tissues after the prolonged use of diphtheric toxins in small quantities, in guinea-pigs. In one of the animals the organs had increased to over four times their normal size. The same phenomena followed injections of Bacillus pyocyaneus. Petit[76] also found hypertrophy to follow filtered cultures of the Löffler bacillus in fishes. That the hypertrophic process is overactive is shown by the fact that hypertrophy also occurs in the remaining gland when one has been extirpated. Stilling[77] observed that in young rabbits the remaining adrenal sometimes attained very large size; Auld[78] also reported several instances in cats. In the presence of these facts it is evident that the adrenals are submitted to excessive activity when certain toxics appear in the blood-stream, and that the local lesions are the expression of a physiological function utilized beyond its normal limits. The histological lesions found post-mortem are no longer pathological manifestations; they are those of physiological overuse or overwork.

[74] Arnaud: *Loc. cit.*, p. 15.
[75] Langlois and Charrin: La Médecine Moderne, Feb. 5, 1896.
[76] Petit: *Loc. cit.*

That we are dealing with the effects of overactivity is sustained by evidence from another direction. In the instances in which hypertrophy was caused by injections of toxins these were administered in small doses at frequent intervals, the process extending over a period of many weeks. If we analyze Wybauw's report, there are points which tend to indicate even more than the direct effects of toxins noted. This author refers to promiscuously distributed swollen cells, the protoplasm of which is less clear than usual, and to other features that recall the characteristics of cloudy swelling observed most frequently in the liver and kidney and in the heart-muscle. This we know may be caused not only by toxins, but also, and with equal frequency, by nutritional disturbances excited by nervous stimulation,—a fact which recalls that electrical stimulation of the splanchnic nerve increases the functional activity of the adrenals.

What these organs are exposed to under excessive stimulation, especially in the course of febrile infections and intoxications, is suggested in the following lines by Lazarus-Barlow;[79] "It is generally held that the cloudy swelling of pyrexial disease and the fatty changes of hyperthermia are to be associated, and many authors hold that cloudy swelling is a transitional stage in the pathological conversion of proteid into fat. It is certainly in favor of this view that cloudy swelling is most commonly

[77] Stilling: Virchow's Archiv, Dec., 1889.
[78] Auld: British Medical Journal, June 3, 1899.
[79] Lazarus-Barlow: "General and Exper. Pathology," p. 414, 1904.

seen in rapidly fatal and acute pyrexial disorders, fatty changes in chronic pyrexial disorders."

Again, we have seen the predominant rôle infections play in adrenal hæmorrhage. We shall now see to what extent the adrenals are the seat of fatty change, which means in this connection the frequency with which these organs are involved in disease:—

Arnaud,[80] alluding to the signs of fatty degeneration in the adrenals observed *post mortem,* writes: "This lesion, which is appreciable only by histological examination, is very common, as shown by my personal researches. It existed *to a more or less marked extent 36 times in 100 subjects* whose adrenals had been collected *at random* at autopsies." Rolleston[81] refers to this subject in the following words: "In the suprarenal bodies of adults *fatty change is so common as to be a physiological condition.* The fat occurs as large globules in the cells. This change may be present throughout the whole of the cortex or be best marked in the zona fasciculata. The medulla is occasionally seen to be occupied by fat, but never to the same extent as the cortex, while in children there is little fat normally. Attlee found, however, some, though slight, fatty change in still-born children. In children dying from marasmus there was marked fatty change, which was more frequent than in the liver. The cortex was affected in all, and the medulla in 6 out of the 9."

Now, if we realize that it is only in febrile diseases and intoxications that cloudy swelling and fatty degeneration occur, and also that the proportion of deaths due to non-febrile processes is relatively large, it will become apparent that *the adrenals must be regarded as exposed to lesions endangering life in all diseases and intoxications attended by a high temperature.*

On the whole, a general summary of the evidence and the conclusions based thereon submitted in the foregoing pages seem to me to have demonstrated:—

1. That the adrenals are greatly exposed, owing to their delicate structure and their location among the great blood-channels of the splanchnic area, to active and passive congestion of a dangerous type;

[80] Arnaud: *Loc. cit.*, p. 6.
[81] Rolleston: Allbutt's "Practice," p. 567.

2. That in the course of any toxæmia the adrenals are liable (a) *to cloudy swelling and fatty degeneration when the temperature and blood-pressure are high, and* (b) *to hæmorrhage when their internal vessels are unable to resist the centrifugal pressure of their blood;*

3. That recovery from infections and toxæmias of all kinds depends to a material degree upon the extent of the lesions to which the adrenals are subjected during the active stage of the disease;

4. That high fever and high blood-pressure, on the one hand, and abnormally low temperature and low blood-pressure, on the other, are the signals that the adrenals are endangered.

THE IMPORTANCE OF THE ADRENALS IN PHYSIOLOGY AND PATHOLOGY.

The foregoing pages have afforded an idea of the importance of the adrenals. We have seen that they were essential to life in man as well as experimental animals; that the secretion was specific as regards its physiological action; that it acted directly on the heart-muscle and the arterioles, and was capable of increasing the contractile power of these organs; that inasmuch as its action was exercised upon the muscular layer of all vessels, the capillaries which are not supplied with such a coat were not acted upon by the adrenal principle; that the capillaries of the adrenals were thus exposed to disruptive congestion and destructive hemorrhages when toxins and other poisons caused an abnormal rise of blood-pressure, and that this danger was enhanced by the presence of organic lesions in the adrenals.

It is with these facts as foundation that I urged in the first edition of this work published in January, 1903, that the adrenals played a far more important rôle in many diseases other than those of the adrenals *per se,* an assertion which applies as well to other ductless glands to be reviewed in the present work. To apprehend the relationship between these organs and the many diseases in which they take part, my own interpretation of their functions must be accepted. This condition is not imposed upon the reader arbitrarily, but because of three cardinal facts which render it unavoidable: (1) that my views are sustained by a far greater number of scientific