curve, they concluded that there had been a strong constriction of the small arteries: strong, in their sense, meaning the relative constriction as compared to that of other vessels. This is fully accounted for by the greater relative supply of muscular tissue in these peripheral vessels. As is well known, arteries are endowed with a coat of muscular fibers, which assumes increased thickness and relatively greater mechanical power as the capillaries are approached; so that in the smaller arteries the muscular layer is relatively quite thick. All the work done in recent years has emphasized the fact that the adrenal active principle enhances the tone of blood-vessels, chiefly that of the *arterioles,*[51a] though not of the coronaries or pulmonary vessels.

That all organs are similarly affected owing to their vascular supply was also shown by Oliver and Schäfer by means of the plethysmograph, not alone the limbs, but such organs as the spleen and the kidney being contracted from 20 to 25 per cent. after intravenous injections of the extract. These experiments also showed that great vascular constriction in the splanchnic area was caused. Veins, we have seen, are likewise constricted by suprarenal extract; they also contain muscular fibers in their thinner walls. Although the supply of muscular elements is less important than in the arteries, this is, to a degree, compensated by the greater lumen. That the entire vascular system of the organism is thus acted upon by the suprarenal specific principle, owing to the muscular tissues which it contains, is beyond question.

Can we conclude from these data that the vasomotor center is never influenced by the suprarenal extract? As will be shown later on, the secretion of the adrenals and adrenal extractives enhance metabolic activity in living cells, including vascular elements. Their action on vessels is thus independent of any upon the vasomotor center except in so far as their influence on general metabolism is concerned, in which case this center would merely be stimulated along with all other tissues.

Briefly, Schäfer's statement that "the intravenous injection of suprarenal extract produces a powerful physiological action upon the muscular system in general, but especially upon the muscular walls of the blood-vessels, and the muscular wall of the

[51a] Swale Vincent: "Internal Secretions and the Ductless Glands," p. 164, 1913.

heart" may be accepted as the basis of the conclusion that *adrenal extract causes cardiac and vascular contraction by stimulating directly the muscular elements of the heart and vessels, and mainly the arterioles.*

Action of the Adrenal Secretion upon the Heart.—The addition of a given proportion of glandular substance to the aggregate contained in the organism, or the removal of some by any method, should involve a corresponding augmentation or a diminution of the normal manifestations that represent suprarenal functions, whatever these may be. The injection of suprarenal extract, we have seen, produces a rapid and marked increase of blood-pressure. When, therefore, we speak of stimulating these structures we imply contraction of the muscular fibers and approximation of the vascular walls toward the center of the blood-stream and as a corollary, increased tension in the veins, with resistance to, and slowing of, the contractions of the right ventricle. Biedl[51b] states in this connection: "The full action of adrenalin may, however, be observed in the mammalian heart *in situ* after the vagal terminals have been paralyzed with atropine. There is, as a rule, a further acceleration of the contractions and there is, especially, a stronger ventricular systole which is well seen by registering the contractions or by means of a plethysmograph. This increased cardiac activity is the result, not of improved circulatory conditions arising out of the heightened blood-pressure, but of the direct action upon the heart of the substance itself. Thus, the intravenous injection of suprarenal extract will bring back life into an animal poisoned with chloral, in which the action of the heart is almost or entirely obliterated. The injection is followed by a progressive increase in the rapidity and *power* of the contractions; the blood-pressure, which had fallen to nothing, rises; and, after a second injection, the heart resumes its normal activity which is maintained. . . . . The action of adrenalin may also be observed in hearts which have been removed from the living body. Oliver and Schäfer experimented with isolated frogs' hearts through which normal saline solution was allowed to circulate. They found that suprarenal extract produces spontaneous contraction in a motionless heart; in the case of a feebly

[51b] Biedl: "Internal Secretory Organs," p. 200, 1913.

beating heart, the beats become stronger and more rapid, the irregularity disappears, and rhythm is restored. . . . . Hering-Bock found that an increase in the pulse-rate and a stronger cardiac contraction also followed the employment of adrenalin in the isolated cardiopulmonary circulation." Briefly, these facts, which summarize the observations of a larger number of experimenters clearly show that *an excess of adrenal extract in the blood increases the contractile power of the cardiovascular system.*

Under these conditions, it seems evident that the blood tends to gravitate toward the periphery.

FUNCTIONAL RELATIONSHIP BETWEEN ARTERIES AND THEIR CAPILLARIES UNDER THE INFLUENCE OF THE ADRENAL SECRETION.—The very marked contractile power that suprarenal extract also possesses over the cardio-vascular muscles plays an important indirect rôle in the organism which seems to have been overlooked so far: *i.e.*, that, *since capillaries are not supplied with muscles (their walls consisting of endothelial plates), they are not contracted as are arteries and arterioles.*

This embodies two kindred prominent features of pathology: *i.e.*, the fact that *when vessels supplied with a muscular coat contract their capillaries dilate* owing to the increased pressure to which the arterial contraction gives rise within the latter, while the opposite relative mechanism—*when vessels supplied with a muscular coat dilate their capillaries contract*—prevails owing to the resiliency of the latter when the blood in them recedes. In other words, while, in the first case, the blood is crowded outwardly, in the second it is crowded inwardly.

The physiological importance of these propositions will be shown in subsequent chapters, but their bearing and soundness seem sustained by the fact that they alone, of all solutions so far advanced, can satisfactorily explain an experimental phenomenon—a true suprarenal paradox—encountered by Langlois and Charrin in the course of their earlier laboratory work.[52] These observers, in order to study the action of suprarenal substance upon toxic agents and toxins, injected equal doses of virulent cultures into two groups of guinea-pigs, the animals constituting one of the groups having each been deprived of one suprarenal gland. The group of *normal* animals

[52] Langlois and Charrin: Comptes-rendus de la Société de Biologie, July 10, 1896.

lived altogether 138 hours; that of *mutilated* animals 150 hours. Several experiments of the same kind were performed; invariably did they find that the animals from which one gland had been extirpated lived longer than those left in their normal condition. The differential contractility of vessels and capillaries referred to render this phenomenon a normal consequence under the circumstances: The caliber of the *muscular* vessels, veins, and arteries of the mutilated animals having become enlarged and their walls relaxed by the loss of suprarenal stimulus, engorgement of the larger trunks occurred, and caused *depletion of the remote capillaries,* including those of the central nervous system. The virulent toxins injected producing their main primary effects upon the latter, and, the quantity of toxic blood transported to them in a given time being smaller than in a normal animal, the longevity of the latter was prolonged in proportion.

I shall frequently refer in subsequent chapters to this relative behavior of vessels under the effects of suprarenal secretion or extract. We will see also that it is an important feature, not only of the physiological action of certain drugs, but also of various toxins, that of the pneumonia bacillus, for example. The conclusion, therefore, that *vessels supplied with a muscular coat and capillaries are antagonistic in contraction and dilation* is only submitted as a postulate for the time being.

TOXINS, POISONS, VENOMS, AND DRUGS IN LARGE DOSES AS INHIBITORS OF ADRENAL FUNCTIONS.

Analogy suggests that, besides the normal standard of suprarenal activity, there must be inadequate activity, physiological to a certain extent, but pathological when extremes are approached. Pending considerable testimony to this effect it is sufficient to recall that insufficiency of the adrenals is now recognized as a clinical entity. We have seen that hæmorrhage into both adrenals can cause death, and we shall see presently that various poisons likewise cause, mainly by variations of the blood-pressure, cessation of the adrenal functions. Is this result due to direct annihilation of the latter by the poison, or must

it be ascribed to some indirect factor, such as the variations of general blood-pressure, caused, as is well known, by many poisons, including certain toxins, and which must necessarily affect the adrenals as well as other organs?

This question may perhaps be elucidated by trying to account for the hæmorrhages that occur as a complication of local disease. These at first seem to afford a ready answer, since the vast majority of them are traceable to organic lesions of the glands that practically annul their efficiency by destroying the greater part of their substance. Partial destruction of the organs and corresponding loss of activity follow each other so logically that any conclusion other than that, in accord with the prevailing view, all poisons, toxins especially, act morbidly upon the adrenal tissues *per se* would seem unwarranted. And yet we have in cerebral hæmorrhage or "apoplexy" evidence to the effect that adrenal hæmorrhage, which Arnaud termed "adrenal apoplexy," might also be due to high general blood-pressure, with rupture of the adrenal vessels, particularly when these vessels are diseased. Again, poisons being carried to all parts of the organ we should, if their action were direct, find the lesion in the functional cellular elements throughout the entire organs. Not only is this not the case, but the lesions *are* essentially vascular.

While studying the pathological histology of suprarenal hæmorrhage, Arnaud found that it was not in the medulla proper, as generally believed, that these hæmorrhages occurred, but in the tissues of the internal cortical zone. In emphasizing this fact, he states: "It is at this point that the *capillaries tear under the influence of a powerful congestion.* When the hæmorrhage is important, it is due to *rupture of one of the branches of the capsular vein* at any point of its walls, and occurs into the medullary substance or into the central conjunctivo-vascular sheath." The medulla proper may be respected to the last, either a capillary peripheral to it, or some part of the intrinsic portion of the vein—probably weakened by the local disease—constituting the yielding structure. Furthermore, Nature seems to protect the last vestiges of the medullary substance even after a localized hæmorrhage. This is suggested by the fact that Arnaud found in such areas evi-

dent signs of organization, at times indicating a local interstitial inflammatory process, at others a retrogressive metamorphosis recalling that observed in hæmatomata. Briefly, using his words: "The normal anatomical elements of the suprarenal gland may be found in a more or less perfect state of integrity, either in the periphery of the growth or at one of its extremities." Toxins would hardly be so selective.

Further analysis of this question elicits the fact that the symptoms which characterize the progress of the primary organic disease of the adrenals differ totally from those attending the hæmorrhage proper. While the former may hardly cause suffering or be totally obscured by the signs of any concomitant disorder present, the symptoms attending hæmorrhage are sometimes violent and sudden, the patient abruptly screaming from excruciatingly intense pain in the abdomen, or dropping at once into apoplectiform coma from which he never rallies. Cerebral apoplexy does not furnish a more vivid picture of the overwhelming effects of hæmorrhage. Yet hæmorrhagic foci in various stages of organization are found at autopsies. Thus, one of Arnaud's cases suddenly fell into apoplectiform coma, and died in 48 hours; the only organs found diseased after death were the adrenals, which contained old hæmatomata, and various more or less organized hæmorrhagic foci which showed that local hæmorrhages into them had repeatedly occurred. The suprarenal substance was entirely destroyed excepting a narrow zone toward the inferior edge of the right organ. The urine, during life, and the kidneys, after death, were found normal. Obviously we cannot well ascribe the acute symptoms to the primary organic lesion, since they appear suddenly, practically without warning, and promptly lead to a fatal issue. Excessive, *i.e.*, disruptive congestion again suggests itself.

Confirmatory evidence is also afforded by the facts that, irrespective of infectious diseases, adrenal hæmorrhage may be caused by cardiac and renal disorders in which high blood-pressure results from purely mechanical causes, and that, as is often the case, fatal adrenal hæmorrhage may occur irrespective of any evidence of local disease or the presence of any bacteria. This is well shown in Andrewe's case, referred to on page 6, in which

neither cultures nor stains showed the presence of pathogenic organisms.

There is good ground for the belief, therefore, that the prevailing view that poisons act directly upon the adrenal tissues does not always apply, *i.e.*, that, *besides the insufficiency of the adrenals caused by disease of these organs, there is a form brought on by the general blood-pressure when this is sufficiently elevated (as in the course of some infections and intoxications) to cause intense congestion of the adrenals and rupture of some of their blood-vessels.*

The morbid influence of high blood-pressure is all the more likely to manifest itself when part of the adrenals have already been destroyed by local disease—since the disruptive pressure is concentrated upon a smaller number of vessels—or when lesions of the vessels, atheroma, for instance, have diminished their power to resist centrifugal pressure. Important in this connection, however, is the fact that, contrary also to the prevailing opinion, there is ground for the belief that hypertrophy of the adrenal secretory tissues, which has been observed by Langlois, Charrin, Petit, Stilling, and others in animals (see page 36) under the influence of injected poisons, does not appear to exert any compensative influence when local disease has destroyed any part of the medullary zone of the gland.

As shown by Langlois, Gourfein, and others, mammals continue to live, when all but one-eleventh of their adrenals had been extirpated—or destroyed by cautery or disease we might add — that, unless some compensative action or some accessory organ be present, death occurs when this limit of normal adrenal substance is reached. It seems logical, therefore, that, were the medulla itself capable of assuming compensatory activity, so large a supply for emergencies (the nature of which will be described later on) would hardly have been provided. If analogy be again accepted as guide, other organs do not compensate for what insufficiency organic disease may produce in them by overtaxing remaining normal structures; collateral chromaffin tissues, supernumerary or accessory organs, vicarious functions, and hypertrophy being all *added* elements, thus constituting either auxiliary resources *per se* or auxiliary resources *plus* compensative growth. Even in the case of the organs

of special sense, where the loss of one organ imposes all the physiological labor upon the other, the existing tissues are not overtaxed; they are brought to their highest proficiency by the increase of nutrition which the additional functional use involves. Whatever evidence we have, therefore, tends to show that the *remaining normal structures of a diseased adrenal are not replaced by new adrenal tissue, and that they are increasingly exposed to disruptive congestion as the local morbid process advances.*

It is because of this that adrenal hæmorrhage is observed with relative frequency in Addison's disease. Moreover, Labazine[53] found experimentally that lesions of the adrenals showed that these organs possessed very little regenerative power. When large portions of the glands were excised no restoration of parenchyma occurred.

Toxics which Produce Congestion or Venous Stasis in the Adrenals.—The list of disorders to which adrenal hæmorrhage has been attributed is steadily increasing. Pneumonia, diphtheria, thrush, variola, scarlatina, tuberculosis, meningitis, cancer, septicæmia, purpura, uræmia, asphyxia (toxic wastes), burns (toxic wastes and detritus), typhoid, jaundice and eclampsia seem, however, to stand out most prominently —all of which present as militant agent either a toxin or some toxic intermediate waste. The effect of burns is illustrated by Arnaud's case, in which sudden death followed a burn of the arm. Andrewes's case, in which death occurred 36 hours after the first symptoms of an acute disease which he thought bore some points of resemblance to hæmorrhagic smallpox, also illustrates this class. In fact, instances such as Andrewes's have so often been noticed by clinicians that Still[54] has proposed a distinct category of cases in which "after an acute illness lasting only two or three days, usually with a purpuric or bullous eruption," death occurs, "and the suprarenal lesion appears to be a part of the fatal issue."

That general intoxication can thus act as an original cause of hæmorrhage has been shown experimentally. Thus, Roger[55]

[53] Labazine: Arch. des Sciences Biologiques de St. Petersbourg, p. 249, vol. xi, 1905.
[54] Still: Lancet, May 7, 1898.
[55] Roger: Berliner klin. Wochenschrift, Jan. 21, 1894.

found that inoculation of the guinea-pig with a culture of the pneumobacillus of Friedländer was followed by profuse hæmorrhage into both capsules, the blood actually bursting through the great capsular vein, or causing necrosis of the surrounding elements by mechanical compression. Langlois[56] also demonstrated that suprarenal hæmorrhage could be brought on by the bacillus pyocyaneus. Charrin[57] found that, by injecting diphtheria toxins into guinea-pigs, congestion—which in some instances reached the hæmorrhagic stage—was not alone caused, but he also observed that small doses used repeatedly and during prolonged periods caused hypertrophy of the organs. Petit[58] also noted, after introducing Löffler bacilli in fishes in which the suprarenal structure is clearly glandular, that all the phases of excessive reaction could be brought on. Hæmorrhagic foci were found by Wybauw[59] in the adrenals of a child which had died of broncho-pneumonia the result of a tracheotomy for croup. Kiesmann found the staphylococcus aureus and albus, and Hamill and Dudgeon the pneumococcus.

That the functions of the adrenals are actually inhibited by these various pathogenic agencies has been shown in various ways. Mott and Halliburton, for example, found that after death from exhausting diseases the proportion of active principle present in the adrenals was either absent or greatly reduced. By ascertaining the relative proportion of chromaffin granules in the adrenals of 50 adults who had died of various diseases. Bainbridge and Parkinson[60] were able to note the absence of the agent in the medulla of the organs of cases which had died of infectious diseases, peritonitis, shock, or where a low blood-pressure had existed. Luksch[60a] ascertained the degree of functional disturbance caused in the adrenals by disease, by ascertaining the relative pressure-raising power of their extracts. While certain conditions, starvation, simple fever, did not show any material change in this direction, various infectious diseases, uræmia and phosphorus poisoning, caused the extracts not to display the normal pressure-raising property.

[56] Langlois: Le Bulletin Médical, Feb. 7, 1894.
[57] Charrin: La Semaine Médicale, June 3, 1896.
[58] Petit: La Semaine Médicale, June 3, 1895.
[59] Wybauw: Annales de la Société Royale des Sciences Méd. et Nat. de Bruxelles, vol. vi, Nos. 2 and 3, 1897.
[60] Bainbridge and Parkinson: British Med. Jour., May 11, 1907.
[60a] Luksch: Wiener klinische Wochenschrift, B. xvii, No. 14, April 6, 1905.

Of course, a certain proportion of these cases may be attributed to exhaustion of the glands during the course of the disease. That the morbid effects are mainly due to excessive variations of the blood-pressure is suggested by the location of the organs, the richness of its blood-vessels, especially of its veins, the proximity of the inferior vena cava, which receives the blood almost directly from the gland on the right side. Pressure during labor upon the inferior vena cava and the suprarenal gland, located, as they are, between the liver anteriorly and the vertebral column posteriorly, may also give rise to congestion of the vessels of the glands and result in hæmorrhage.

Various drugs may bring on hyperæmia, congestion, and hæmorrhage of the suprarenal glands, as shown by Pilliet,[60b] who observed these phenomena after the use of nitrate of uranium. Essence of cloves has also been found capable of stimulating them to such a degree as to bring on macroscopically visible lesions.

On the whole, the conclusion seems warranted that *so many toxic substances cause adrenal hæmorrhage that a common effect of all these poisons on the general blood-pressure, sufficient to cause active or passive congestion or venous stasis in the adrenals, is necessary to explain the genesis of this class of cases.*

Increased Functional Activity of the Adrenals as a Predisposing Cause of Adrenal Hæmorrhage.—The view that the adrenal specific principle itself possesses antitoxic powers has suggested to those who have accepted it the conclusion that a high degree of toxæmia, by overtaxing the organs, caused congestion, and, if this reached beyond certain limits, hæmorrhage. This conception was mainly based on the view of Brown-Séquard, who was led, by the toxic effects of blood taken from decapsulated animals upon normal ones, to ascribe to the *glands themselves* a direct antitoxic function. It met with further support in the fact that violent toxæmia invariably follows the removal of both organs, and was therefore accepted by many investigators. It was also maintained by Dubois,[61] who, having isolated toxic alkaloids from adrenal substance identical in some of their reactions with muscle-toxins, concluded

[60b] Pilliet: Le Bulletin Médical, Feb. 7, 1894.
[61] Dubois: Archives de Physiologie norm. et path., vol. viii, 1896.

that the adrenals occluded products of organic waste and modified them *in situ,* but that they did not seem to secrete any special substance destined to enter the circulation. This view has not withstood any degree of close scrutiny. The destruction of poisons *within* the adrenals themselves involves the passage of the systemic blood through their cellular elements. When in the cadaver we note the relative dimensions of all the vessels within a narrow radius of the adrenals, it becomes apparent that the conditions are not such as to indicate a provision for the passage of the blood through these organs. Moreover, if the adrenals were intended to destroy toxics in the blood traversing them, the afferent channels would normally contain blood from all parts of the organism and charged with toxic elements, while the efferent channels would convey the purified blood charged with the suprarenal secretion to the heart, ready for redistribution. Instead of this the afferent vessels receive their blood from the aorta,—arterial blood,—while the efferent vessels pour their blood into the vena cava. But, as shown by Alezais and Arnaud[62] in 1890, this blood is *also arterial.* We thus have a short arterial circuit, or loop, which, besides furnishing the adrenals their intrinsic and functional blood-supply, evidently has for its purpose the immediate return to the general circulation of a small quantity of arterial blood charged with what Claude Bernard (1867) has well termed an "internal secretion."

More in keeping with experimentally established facts are the views which attribute to the secretion itself, when in the blood-stream, the antitoxic functions referred to. Thus, Abelous and Langlois,[63] after a series of careful experiments, reached the conclusion that their normal function was to elaborate an internal secretion capable of neutralizing or destroying the poisonous substances resulting from muscular contractions: a fact further demonstrated to them by the mitigating effects of injected suprarenal extract. Some years later these observers[64] amplified their views and concluded that, after removal of both adrenals, there was a true auto-intoxication, the animals generating poisons which were normally

[62] Alezais and Arnaud: Quoted by Arnaud, *loc. cit.*, p. 34.
[63] Abelous and Langlois: Archives de Physiologie norm. et path., vol. iii, p. 267, 1892.
[64] Abelous and Langlois: "Travaux de Laboratoire," Lancet, Aug. 20, 1898.

either destroyed or changed in the interior of the glands or by material formed by the organs and poured into the blood. The poisons, they thought, were probably products of muscular activity and also of bacterial origin, and exerted a special influence on the heart and circulatory system. Mosse[65] also believed that the adrenals produced a stimulating substance and that they could simultaneously neutralize poisons formed in various parts of the organism.

Reasoning by analogy, we can surmise that the metabolism of the organs is principally maintained by the passage of blood through them and that the internal secretion represents the physiological product of their metabolism. Under these circumstances, the quantity of blood in them at a given time would stand as the controlling factor, the quantity of active principle secreted into the general circulation being proportionate to this quantity. Have we any ground for the belief that the circulation alone may keep up the suprarenal functions? The experiments of Soddu[66] seem to throw light upon this question. In order to ascertain the rôle of the suprarenal peripheral nerves, this investigator isolated the glands of several dogs from their external connections, leaving only the blood-vessels. Although eight animals were submitted to this operation, none died, and all, after a few days, were in their normal health. It is evident that, if the blood alone can thus sustain the life of the organs, an increased flow into them—under, perhaps, the influence of toxic blood upon the centers of their nerve-supply—will involve a corresponding increase of functional activity. That very large or overwhelming doses of any poisonous agency should produce the contrary effect and arrest the functions of the adrenals by annihilating those of their center is suggested by the pathogenesis of suprarenal hæmorrhage.

Still, this involves the existence of an intrinsic nervous supply capable of producing an increased flow of blood into the glands under the stress of an acute toxæmia and a corresponding increase of vascular tension. By suddenly calling the suprarenal functions into violent activity, an excessive dose

[65] Mosse: Fortschritte der Medicine, No. 21, 1897.
[66] Soddu: Lo Sperimentale, No. 2, 1898.