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## CHAPTER I.

THE ADRENALS IN CLINICAL PATHOLOGY  
AND THERAPEUTICS.SIMILARITY OF THE EFFECTS OF REMOVAL OF THE ADRENALS  
IN ALL VERTEBRATES, INCLUDING MAN.

BROWN-SÉQUARD,<sup>1</sup> in 1856, demonstrated the physiological importance of the suprarenal capsules by showing that removal of these organs from animals was soon followed by death. To offset the conclusions of Phillipeaux and Gratiolet, who ascribed death to secondary involvement of the central nervous system, he extended his researches,<sup>2</sup> and showed, first, that transfusion of blood taken from a normal animal into a dying, decapsulated animal brought the latter to life, and, second, that the blood of a dying, decapsulated animal was poisonous to another decapsulated animal, the life of the latter being shortened by eight hours as compared to the average longevity of other animals similarly mutilated.

A certain degree of antagonism to Brown-Séquad's conclusions long prevailed among a limited number of investigators, who ascribed death in animals from which both adrenals had been extirpated to surgical shock—a view apparently sustained by the close relationship that exists between these organs and the sympathetic system. That such may be the case under some circumstances: *i.e.*, the use of an animal debilitated by starvation or rough handling, lack of dexterity in the extirpation of the organs, is to be surmised; but, when all features that tend to compromise the issue are absent, there is not the least ground for the view that shock is the cause of death in decapsulated animals. As shown by Langlois,<sup>3</sup> no marked symptoms usually occur during the first twenty-four hours. The fatal

<sup>1</sup> Brown-Séquad: Comptes-Rendus de l'Académie des Sciences, vol. xviii, 1856.

<sup>2</sup> Brown-Séquad: Journal de Physiologie, vol. 1, 1858.

<sup>3</sup> Langlois: Archives de Physiologie norm. et path., vol., 1897.

issue is not immediate; and in frogs, rabbits, guinea-pigs, and dogs the post-operative life varies from an average of forty hours in mild weather to twelve or thirteen days in the hibernating frog in winter. In a series of fifty-nine rats from which Boinet<sup>4</sup> removed both adrenals, four lived several months. Some evidence of shock should have appeared in at least a small proportion of the operated animals. Not only was this not the case, but the fact that in four of them the prolongation of life was found to have been due to accessory or compensatory organs demonstrates the weakness of the shock hypothesis as the main cause of death in decapsulated animals. Furthermore, the average symptomatology of post-operative life in various species—inco-ordination, muscular weakness or excitement, and tremors; then paralysis of the hind-quarters, with gradual involvement of the trunk and upper extremities, contraction of the pupil, gradual and steady slowing of the cardiovascular rhythm, convulsions, hæmaturia, epistaxis, etc.—in no way resembles that of shock.

Finally, complete removal of but one organ seems to affect animals so slightly that they appear to suffer no inconvenience; they continue to live month after month, "quite well and active"; *i.e.*, until the experimenter removes the second adrenal, when death occurs within thirty-six hours. This fact, added to many others elucidated by the labors of Abelous and Langlois,<sup>5</sup> Oliver and Schäfer,<sup>6</sup> Cybulski,<sup>7</sup> Szymonowicz,<sup>8</sup> Gourfein,<sup>9</sup> Langlois,<sup>10</sup> Swale Vincent,<sup>11</sup> Boinet,<sup>12</sup> Parhon and Golstein,<sup>13</sup> and others, shows that there is no legitimate ground—after eliminating all factors that obviously tend to disguise the source of physiological phenomena and pervert their meaning—to doubt that, as Brown-Séguard was first to show, extirpation of both

<sup>4</sup> Boinet: *Marseille Médical*, Sept. 1, 1899.

<sup>5</sup> Abelous and Langlois: *Archives de Physiologie norm. et path.*, vol. xiii, p. 267.

<sup>6</sup> Oliver and Schäfer: *Journal of Physiology*, vol. xviii, 1895.

<sup>7</sup> Cybulski: *Gazeta Lekarska*, March 23, 1895.

<sup>8</sup> Szymonowicz: *Archiv f. d. Gesam. Phys.*, vol. lxiv, 1896.

<sup>9</sup> Gourfein: *Revue Médicale de la Suisse Romande*, March, 1896.

<sup>10</sup> Langlois: *Loc. cit.*, 1898.

<sup>11</sup> Swale Vincent: *Journal of Physiology*, Sept. 11, 1897; Feb. 17, 1898; Apr. 25, 1898.

<sup>12</sup> Boinet: *Loc. cit.*

<sup>13</sup> Parhon and Golstein: "Les Sécrétions Internes," p. 736, 1909.

suprarenals is followed by death, and that these organs fulfill in the organism a rôle of great physiological importance.

Are the suprarenal glands functionally as important in man as they are in the lower vertebrates? The clinical field alone offers the necessary elements for the study of this question; but it is strewn with obstacles. The various kinds of neoplasms which develop in these organs, with the possible exception of sarcoma, are of slow growth; the sufferer passes through various phases that are more or less influenced by concomitant conditions and by the pressure which the tumor exerts upon important neighboring structures. In carcinoma there may also be involvement of other viscera by continuity of tissue or metastasis. We therefore obtain, in relation to the symptom-complex of pure suprarenal origin, a transformed picture, one that precludes all certainty as to the relations between cause and effect. Addison's disease affords, if anything, less opportunity for solid analysis; it may be associated with suprarenal lesions and it may not; in some cases but one organ is involved; in others, both; if it is due to suprarenal tuberculosis, this process may be secondary or primary, thus furnishing a series of misleading symptoms due to the extrinsic lesions; finally, we may at a *post-mortem* find the organs completely destroyed and obtain an *ante-mortem* history in which the Addisonian syndrome is conspicuously absent.

What is required for a fruitful analysis of this question is a condition in which the adrenals are alone the seat of a mortal lesion: a lesion capable of suddenly annihilating the functions of both organs precisely as does their experimental removal in animals. A single disorder of the adrenals, among the few that have been so far described, fulfills these requirements in some of its manifestations, namely: hæmorrhage. The literature of this subject is, however, exceedingly meager: hardly two hundred cases having been reported. We are therefore fortunate in having at our disposal an able and exhaustive review of eighty of these cases, including several of his own, by François Arnaud,<sup>14</sup> of Marseilles, which affords the necessary data. While some of the cases are very briefly reviewed, the

<sup>14</sup> François Arnaud: *Archives Générales de Médecine*, p. 64, July, 1900.

details furnished are at least sufficient to enable us to obtain what appears to be strong evidence to the effect that, precisely as it does in the lower animals, destruction of the adrenals in man causes death within a very brief period.

Indeed, out of the eighty cases collected by this investigator, death occurred within a period ranging from a few hours to three days in fifteen. In all of these the pathological data given show that both glands had been the seat of the hæmorrhagic process: of "suprarenal apoplexy," as he terms it. Ten of these cases, however, lose some of their value as testimony because no allusion is made to the condition of the other organs. In the other five, including details that we have obtained from the original reports, it is specifically stated that *lesions were found nowhere else in the organism*. To the following tabulated list of these cases I have added two instances of the same kind (Andrewes and Colman):—

CASE 1 (Arnaud<sup>15</sup>).—Male, 36 years. Death occurred 48 hours after entrance. Both glands were apoplectic and greatly enlarged. One weighed 28½ grammes; the other 48 grammes. Both when cut resembled flesh, and were studded with hæmorrhagic foci and spots of hæmatomatous organization indicating a progressive lesion of long standing. A small amount of medullary substance was still present in the right capsule, but otherwise the organs were structurally destroyed.

CASE 2 (Arnaud<sup>16</sup>).—Female, 17 years. Death occurred suddenly on the eleventh day after the receipt of a burn on the arm; the symptoms suggested acute poisoning, but the autopsy revealed hæmorrhage into the right capsule and congestion of the left.

CASE 3 (Andrewes<sup>17</sup>).—Female, 15 months. Death 36 hours after onset of symptoms. Both capsules showed interstitial hæmorrhage. All cultures were sterile, or, if any organisms were present, not one grew on ordinary media or stained with ordinary reagents.

CASE 4 (Mattei<sup>18</sup>).—Male, aged 60 years. Death in 24

<sup>15</sup> Arnaud: Archives Générales de Médecine, pp. 16 and 53, July, 1900.

<sup>16</sup> Arnaud: Archives Générales de Médecine, p. 50, July, 1900.

<sup>17</sup> Andrewes: Lancet, May 7, 1898.

<sup>18</sup> Mattei: Lo Sperimentale, 1863. Case I in Trans. Gaz. hebdom., Paris, No. 35, p. 330.

hours after onset of acute symptoms. Both capsules were enlarged, and transformed into bags containing clots surrounded by the cortex, which had thus been forcibly detached from the medullary substance.

CASE 5 (Garrod and Drysdale<sup>19</sup>).—Case, aged 4 months. Brought into hospital dead. Both glands dark-purplish red, though not enlarged; meshes of stroma filled with red corpuscles.

CASE 6 (Droubaix<sup>20</sup>).—Case, 11 hours old at onset of symptoms. Death in 3 days. Hæmorrhage into both organs, with infiltration into the pericapsular cellular tissue.

CASE 7 (Colman<sup>21</sup>).—Case, 11 months. Death in about 25 hours. Both capsules showed diffuse interstitial hæmorrhage, and cultures proved sterile.

Strongly suggestive, also, is the fact that, of the seventeen cases of comparatively sudden death, fifteen showed suprarenal apoplexy in both organs, while two only showed involvement of but one organ. These two instances might invalidate the evidence adduced, could the sudden death in them not be shown to have been due to other causes. But such is the case: In the one (Parrot's<sup>22</sup> case No. 11) the hæmorrhagic adrenal had ruptured, and the patient died of hæmorrhage into the peritoneal cavity; in the other (Droubaix's<sup>23</sup> case No. 9) death had resulted from uræmia, due to granular and cystic degeneration of the kidneys.

Additional evidence is afforded by the fact that complete destruction of but one adrenal proves harmless to man, as it does in animals. The results of operative procedures instituted for the removal of suprarenal neoplasms prove this to be the case. A lipomatous capsule, for instance, was removed, along with a wedge-shaped piece of underlying kidney, by Mayo Robson<sup>24</sup> in 1897. "The wound healed by first intention and the patient rapidly regained her lost flesh and strength. She remains well, and had had no return of the trouble." This

<sup>19</sup> Garrod and Drysdale: Lancet, May 7, 1898.

<sup>20</sup> Droubaix: Thèse de Paris, Case I, p. 26.

<sup>21</sup> Colman: Lancet, May 7, 1898.

<sup>22</sup> Parrot: Archives Générales de Médecine, vol. xcix, 1872.

<sup>23</sup> Droubaix: Thèse de Paris, 1887.

<sup>24</sup> Mayo Robson: British Medical Journal, Oct. 21, 1899.

report was published almost two years after the operation. A fibromyxosarcomatous adrenal was removed, along with the entire right kidney, by Howard A. Kelly.<sup>25</sup> The case proceeded to full recovery notwithstanding the malignant nature of the growth. A tuberculous adrenal and the right kidney were also removed by A. F. Jonas.<sup>26</sup> The patient was discharged six weeks later in full convalescence. Finally, Knowsley Thornton<sup>27</sup> removed a sarcomatous gland from a woman aged 56 years. The patient was seen six years later and found in good health.

This does not mean, however, that a diseased gland may not cause death. In this particular the adrenals are similar to any other organ. A rapidly growing sarcoma or a carcinoma may start in one of the organs, develop by metastasis elsewhere, and cause death. Tuberculosis frequently finds a *nidus* in either adrenal or both simultaneously; this process, along with the asthenia engendered by the suprarenal disease, may rapidly end in death. Again, when we consider the frequency with which fatty degeneration is found in these organs when microscopically examined,—thirty-six times out of one hundred autopsies taken *at random*, according to Arnaud,<sup>28</sup>—it would certainly be unwise to establish such limits.

But this also suggests that death may thus follow any destructive process (hæmorrhage included) of a single adrenal, if the functions of its mate are sufficiently inhibited through a local lesion or by a morbid condition involving its peripheral vascular or nervous supply. Indeed, the anatomical relations of these glands indicate that their functions are primarily dependent upon the integrity of these trophic structures. The multitude of nerves distributed to them include medullated fibers from the solar plexus, the sympathetic's densest network. Dogiel<sup>29</sup> states that the internal zone of the cortex is surrounded by a more or less dense fibrillary plexus, and that the medullary substance is provided with an extraordinary sup-

<sup>25</sup> Howard A. Kelly: Quoted by Ramsay, Johns Hopkins Hosp. Bull., Jan., Feb., Mar., 1899.

<sup>26</sup> A. F. Jonas: Annals of Surgery, April, 1898.

<sup>27</sup> Knowsley Thornton: Harveian Lectures.

<sup>28</sup> Arnaud: *Loc. cit.*, p. 6.

<sup>29</sup> Dogiel: Archiv f. Anatomie u. Physiologie, p. 90, 1894.

ply of nerves. He likewise found the aggregate of these nerve-fibrils to be greater than that of the glandular elements proper. It seems evident, therefore, that any organic lesion affecting or involving the peripheral nerve-structures of one organ—tuberculosis, cancer, etc.—can so compromise its functions as to make it practically useless if suddenly called upon by hæmorrhage into its mate to assume the physiological rôle of both.

All these facts appear to demonstrate that in man, as well as in the lower vertebrates, life continues as long as one of the adrenals is normal, or, at least, as long as any morbid condition affecting this organ intrinsically or extrinsically is not sufficiently advanced to materially compromise its physiological functions. But, as is also the case in lower vertebrates, man soon dies if the physiological functions of both organs are arrested through any intrinsic or extrinsic disorder, unless some compensating organ or condition be vicariously active. It seems evident, therefore, that *the physiological functions of the adrenals are sufficiently similar in all vertebrates to warrant the use of experimental data obtained with lower animals in the study of these organs in man.*

#### FUNCTIONS OF THE ADRENALS THAT ARE SUPPRESSED WHEN THESE ORGANS ARE REMOVED.

Cybulski and Szymonowicz<sup>30</sup> found that blood drawn from the suprarenal vein gave rise, when injected into the bloodstream of normal animals, to manifestations similar to those observed after the injection of suprarenal extract. As a controlling experiment, these observers also injected blood taken from veins other than the suprarenal, but with negative results. Langlois<sup>31</sup> corroborated these observations as regards the effects of blood obtained from the suprarenal vein. Dreyer<sup>32</sup> reached the same results, though not in all animals: a feature of his experiments easily accounted for by the known fact, applicable to all glands, that the amount of substance produced by the organs may vary at different times and under different

<sup>30</sup> Cybulski and Szymonowicz: *Loc. cit.*

<sup>31</sup> Langlois: Archives de Phys. norm. et path., p. 152, 1897.

<sup>32</sup> Dreyer: Am. Jour. of Physiol., vol. ii, p. 203, 1899.

circumstances. This obviously suggests that the morbid phenomena witnessed after extirpation of the adrenals are due to the absence of a substance produced by these organs and secreted into the adrenal veins. In his recent work, Swale Vincent<sup>32a</sup> states that considerable evidence attests to the fact that "it passes by way of the adrenal veins into the general circulation."

Not only do the adrenals produce the blood-pressure-raising substance the lack of which accounts for the symptoms that follow bilateral removal, but the secretion of these organs alone possesses the property of arresting these symptoms. Cybulski<sup>33</sup> found experimentally that the increase of blood-pressure and other cardio-vascular manifestations, etc., could not be obtained from similar preparations from the brain, spinal ganglia, lymph-glands, liver, spleen, kidney, testicle, or thyroid. Mankowsky<sup>34</sup> corroborated these observations and noted that the blood-pressure-raising power was peculiar to the suprarenal extract, his experiments having also shown that this action could not be obtained from the fresh thyroid gland, pancreas, lymphatic glands, parotid, kidneys, liver, spleen, cerebrum, heart, or skeletal muscles.

An extract obtained from human adrenals possesses similar properties to the preparations in general use. This important fact was ascertained by Guinard and Martin, of Lyons,<sup>35</sup> who conducted a series of experiments with the adrenals of a healthy executed criminal. Expressed juice of these glands "produced physiological phenomena similar to those noted with the extracts from organs obtained from other animals. The nature of the poisons contained in them did not appear to differ."

The following conclusions appear warranted:—

1. *Removal of both adrenals arrests the supply of a secretion which these organs pour into the adrenal veins.*
2. *The secretion of the adrenals gives rise to physiological phenomena which are not awakened by extracts of other organs.*

<sup>32a</sup> Swale Vincent: "Internal Secretion and the Ductless Glands," p. 232, 1913.

<sup>33</sup> Cybulski: *Loc. cit.*

<sup>34</sup> Mankowsky: *Russian Archives of Physiology and Bact.*, March, 1898.

<sup>35</sup> Guinard and Martin: *Journal de physiologie et de path. génér.*, 1899; *Archives générales de médecine*, Oct., 1899.

#### EFFECTS OF THE ADRENAL SECRETION ON THE CARDIO-VASCULAR SYSTEM.

THE ADRENAL SECRETION AND THE CARDIAC MUSCLE.—While removal of both adrenals is followed by a great fall of blood-pressure and very feeble and rapid cardiac action, intravenous injections of suprarenal extract invariably cause marked increase of the blood-pressure and equally marked slowing of the heart-beat. The blood-pressure increase thus appears to be due to the direct effect of the specific suprarenal principle; but to account for the slowing of cardiac action we are led to implicate the inhibitory action of the vagus. If the bulbar center of this nerve be paralyzed by atropine, however, or the vagus itself be cut, this inhibition ceases and quickening of the heart-beat follows, accompanied by a still greater increase of blood-pressure. Oliver and Schäfer found<sup>36</sup> that the inhibitory action of the vagus under the influence of adrenal extract was sufficient to arrest the auricles for a time, the ventricles continuing to contract slowly.

Mooted points have arisen in this connection that have entailed considerable divergence among physiologists; and, curiously enough, when the various views entertained are analyzed, none of them seem to harmonize with available experimental data.

Cybulski,<sup>37</sup> after a series of careful experiments, reached the conclusion that suprarenal extract acted upon the vaso-motor centers of the medulla and spinal cord, first stimulating, then paralyzing, them. Oliver and Schäfer,<sup>38</sup> after equally careful experiments, concluded that the extract caused powerful constriction of the arterioles by a direct action on their walls, and stimulated the inhibitory center. To this they ascribed the slowing of the heart observed before the vagi were cut, and physiologists have generally accepted the conclusion that the inhibitory center is stimulated. Indeed, even the more recent—and carefully conducted—physiological researches have sustained this opinion; Wallace and Mogk,<sup>39</sup> for instance, were

<sup>36</sup> Oliver and Schäfer: *Journal of Physiology*, xviii, 1895.

<sup>37</sup> Cybulski: *Gazeta Lekarska*, March 23, 1895.

<sup>38</sup> Oliver and Schäfer: *Journal of Physiology*, vol. xviii, p. 230.

<sup>39</sup> Wallace and Mogk: *American Physiological Society Proc.*, Dec. 28, 1898.

led by unquestionable experiments to conclude that the suprarenal extract stimulated the vagus center, thus inhibiting the heart.

A second set of divergent views refers to the nervous structures involved when the heart is separated from its inhibitory center by section of the vagus. The influence of the extract, in this connection, is ascribed by Mankowsky<sup>40</sup> to stimulation of the cardiac and respiratory centers; by Gottlieb,<sup>41</sup> to the direct stimulating effects of the substance upon the intrinsic cardiac ganglia; by de Cyon,<sup>42</sup> to some action upon the vasoconstrictor nerves and simultaneously upon the central and peripheral ends of the cardiac accelerators; by Velich,<sup>43</sup> to stimulation of the vasoconstrictors; and finally by other observers to various more or less complicated combinations which all include some part of the nervous system as the seat of primary effect. By inference, therefore, we are led to look upon this system as the one upon which the specific principle of the adrenals acts physiologically.

A leading question, which embodies the divergent views of Cybulski, on the one side, and Oliver and Schäfer, on the other, resolves itself into this: Does the suprarenal active principle act at all upon the inhibitory centers?

It may prove useful in this connection to recall that, according to prevailing doctrines, the functions of the heart are governed by two sets of nerve-fibers. The one set, derived from the sympathetic, increases the vigor of the heart-beat and tends to quicken the number of beats in a given time. The other set, which arises from the vagus, inhibits the vigor of the heart-beats and their rate or rhythm. Both these "augmentor" and "inhibitor" fibers receive their impulses from the medulla oblongata and from a limited area of the upper portion of the cord, and represent the external, or extrinsic, motor-supply of the organ. Again, the medulla and the spinal area referred to receive impulses—including reflex impulses—from all parts of the organism, including the heart proper, and there is thus

<sup>40</sup> Mankowsky: Russian Archives of Pathology, Clinical Med., and Bact., vol. v, No. 3, March, 1898.

<sup>41</sup> Gottlieb: Archiv für exp. Path., Bd. xxxviii, 1896.

<sup>42</sup> De Cyon: Pflüger's Archiv für Physiol., vol. lxi, p. 370, 1898.

<sup>43</sup> Velich: Wiener med. Blätter, Nov. 11, 1897.

established a cycle of afferent and efferent impulses of which the medulla and the portion of the cord immediately below it represent the center. The effects of destruction of these structures can easily be foretold. As shown by Stricker nearly forty years ago and by other physiologists since, extirpation of the cervical and dorsal portions of the cord causes arrest of the heart's action. When to this is added destruction of the medulla, the certainty of immediate death is but enhanced. Again, certain agents—chloral hydrate, for instance—are known to abolish the functional activity of the cord and to affect the heart as if the vagus had been severed.

Applying these classical data to the question in point, it becomes evident that, if the inhibitor or augmentor centers were directly or reflexly stimulated by suprarenal extract, the effects of extirpation of these centers or of the cord would not be counteracted by its use *since there would be no center to receive and transmit impulses*. The arrest of the heart's action would therefore be permanent.

But experiments have shown that the injection of suprarenal extract at once causes this organ to resume its beat notwithstanding total extirpation of the entire cord. Thus, Biedl<sup>44</sup> cut the medulla oblongata and removed the entire cord of mammals; and, when the blood-pressure had become reduced to 9 millimeters, injected suprarenal extract. This at once brought up the pressure to 160 millimeters. Gottlieb<sup>45</sup> chloralized rabbits until the heart-beats became irregular and excessively slow. An injection of suprarenal extract at once restored the regularity and volume of the pulse. He tried the same experiment when the pulse was no longer registrable by the manometer; a similar result was obtained, and the heart almost immediately resumed its normal action. Isaac Ott<sup>46</sup> etherized a rabbit, cut the cord above the atlas, severed all the cardiac nerves in the neck, and verified the section of the cord *post mortem*. Injections of suprarenal extract were then used repeatedly as soon as the pressure became greatly lowered. They brought it up from 24 to 144 the first time, from 17 to

<sup>44</sup> Biedl: Wiener klin. Wochenschrift, Bd. ix, 1896.

<sup>45</sup> Gottlieb: Archiv für exp. Path. und Phar., Bd. xxxviii, 1896.

<sup>46</sup> Isaac Ott: Experiment No. 11, Medical Bulletin, Jan., 1898.

134 the second, and from 24 to 124 the third time, the interval between the injections of extract and the highest-pressure marks ranging from fifteen to thirty seconds.

These experiments, to which others of a similar kind could be added, speak for themselves. They distinctly show that, contrary to the conclusions of Cybulski, Wallace and Mogk, Mankowsky, Gottlieb, and other observers, *the inhibitory centers are not directly stimulated by the suprarenal extract.*

And, indeed, their conclusion is apparently justified, if removal of the medulla and cord is left out of consideration, and with injections of suprarenal extract as an only guide. In other words, to the question—does suprarenal extract directly affect the cardio-inhibitory centers?—an affirmative experimental result on injecting it into mammals—slowing of the heart—would always be obtained, while the crucial test—section of the vagus—would at once confirm the conclusions previously reached by causing great increase in the rapidity of the heart's action. But division of the cardiac nerves in the neck, including the vagus, and of the cord in no way preventing the action of the extract, the only logical deduction that imposes itself is that *the suprarenal extract exercises a stimulating action directly upon the cardiac muscle irrespective of any action upon the inhibitory centers.*

THE ADRENAL SECRETION AS CONSTRICTOR OF MUSCULAR ELEMENTS.—The last deduction implicates other phases of the question. Prominent among these is the effect ascribed to adrenal extract upon the vasomotor system by various physiologists and clinicians. Is there any such action? Veins—which are but little, if at all, influenced by the cardiac impulse in respect to their rhythmical changes of caliber, the blood before reaching them having to penetrate the capillary system—are distinctly contractile. This may be clearly seen by examining the great veins opening into the heart, and in those of bats' wings. Granting, as is generally taught, that veins are not endowed with a vasomotor supply, we find that they nevertheless contract under the influence of suprarenal extract. Szymonowicz<sup>47</sup> observed that the pressure rose and fell in the external jugular vein, along with the pressure caused in the

<sup>47</sup> Szymonowicz: Archiv für die gesam. Physiol., Bd. lxiv, 1896.

arteries by injections of this substance. Auld<sup>48</sup> states that, when suprarenal extract was injected into a vein "which had been clamped as high as practicable, on releasing the vein after a few minutes a marked diminution of pressure was recorded as compared with that produced by injection into the free vein." This shows a direct action on the vein while the extract was held *in situ* by clamping. Meyer<sup>49</sup> found that a weak solution of epinephrin caused contraction of detached strips of jugular vein; Gunn and Chavasse<sup>50</sup> and Crawford and Twombly<sup>51</sup> obtained similar effects on other veins. This tends to disprove the need of vasomotor nerves to contract such vessels.

While it is obviously difficult to account for the *general* increase of vascular pressure caused by the extract without including vasomotor nerves in the process, a direct action upon the vascular muscles themselves *might* underlie the result attained: a question which can only be elucidated by stripping the vessels of all their nervous connections and then watching the effects of the extracts. This procedure has been resorted to by Oliver and Schäfer, and these physiologists have shown that a vessel will contract after all the nerves to it are cut. Even a freshly excised vessel—one, therefore, obviously freed of all nervous influence—will respond to the contracting effects of an aqueous solution of suprarenal extract, and, if a large vessel be used for the experiment to render the change of caliber more appreciable, the diameter will be found reduced nearly one-sixth. Furthermore, these investigators have found that it acts directly on the muscles of the blood-vessels, and that this action occurs equally well *after section of the cord*. As we have seen, destruction of the adrenals or annihilation of their functions is followed by extreme muscular weakness; this normally led them to the conclusion that all varieties of muscle—the striated, non-striated, and the cardiac muscle (which histologically partakes of both kinds of muscular tissue)—are stimulated.

Observing also that the latter caused a rapid increase of blood-pressure, and that it gave a steep rise to the kymograph-

<sup>48</sup> Auld: British Medical Journal, June 3, 1899.

<sup>49</sup> Meyer: Zeitschrift für Biologie, Bd. xlviii, p. 380, 1906.

<sup>50</sup> Gunn and Chavasse: Proceedings Royal Society, Series B, vol. xxxvi, 1913.

<sup>51</sup> Crawford and Twombly: New York Medical Journal, Aug. 16, 1913.