ACTIVE COOPERATION BETWEEN THE PHYSIOLOGIST AND THE CLINICIAN AND COMPARATIVE ANALYSIS OF COORDINATED DATA IN THE STUDY OF THE INTERNAL SECRETIONS*

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The purpose of our Association being the study of the internal secretions, you will surely realize that it would give me great pleasure to initiate this, our first scientific meeting, with at least an outline of the great progress accomplished in recent years. Unfortunately, my remarks will rather tend in the opposite direction, although my purpose, I hasten to state, is to suggest ways and means that may enable us to hope at least, for a better outlook.

It happens to have been my lot, in addition to active practice, to edit works which aimed to collate, either in logical sequence, or in encyclopedic form, the progress recorded in the medical literature. This class of work, which has taken up much of my time and labor during the last thirty years, involved a review of all the branches of medicine, including the specialties, fifteen times. From its very start, in 1887, I became impressed with the thought that closer cooperation between the clinician and the physiologist would tend greatly to elucidate our knowledge of disease. Each of the nine series of my Annual of the Universal Medical Sciences will, in fact, be found to contain admirable reviews of the contributions to physiology during the corresponding years, by Prof.

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H. Newell Martin, of Johns Hopkins, up to 1890, and by Prof. W. H. Howell, his successor, up to 1896. Unfortunately, the panic of the early nineties, by undermining the resources of the work, imposed the elimination of the department of physiology, with others devoted to auxiliary subjects, from its successor, the Analytical Cyclopedia of Practical Medicine. This is mentioned only to illustrate the importance I have always attached to the active cooperation I urge. Indeed, to us, clinicians, who are responsible for the multitude of lives entrusted to our care, physiological data are as many precious additions to those garnered at the bedside, in the pathological laboratory and through our therapeutic results, for the elucidation of the complicated problems that are constantly surging up before us. For, after all, what is the condition we term "disease," however caused, but "pathological physiology," as Bouchard has well termed it?

Indeed, so close is his connection with physiological problems in his daily contact with disease that the physician sometimes discovers a solution. Thus, a great physiologist, Professor Pawlow, of Petrograd, wrote sixteen years ago (1), after referring to the discovery of gastric secretory nerves: "Physiologists, on the other hand, had fruitlessly endeavored for decades to arrive at definite results upon this question. This is a striking, but by no means isolated, instance where the physician gives a more certain verdict concerning physiological processes than the physiologist himself; nor is it indeed strange. The world of pathological phenomena is nothing but an endless series of the most different and unusual combinations of physiological occurrences which never
make their appearance in the normal course of life. It is a series of physiological experiments which Nature and life institute, often with such an interlinking of events as could never enter into the mind of the present-day physiologist, and which could scarcely be called into existence by means of the technical resources at our command. Clinical observation will consequently always remain a rich mine of physiological facts."

The broad field of endocrinology is in a great measure based on clinical findings, and time may show that the very obscurity which surrounds the whole subject at the present time, is due to the fact that we have too freely ignored the inspirations, in conjunction with physiological discoveries, of the morbid processes that Addison, Graves, Marie, Lau-nois, Frölich and others have described. I shall illustrate later in the course of my remarks, by a few examples among the many available, the elucidative value of clinical data in physiological questions. It will serve to emphasize anew the material advantage that would accrue from closer cooperation between the physiologist and clinician than now prevails—an opportunity greatly facilitated by our Association and particularly through its organ, Endocrinology.

The ways and means favoring such a cooperation being thus available, how should we use physiological and clinical data in our search for truth? Again, time being an important element, in view of the growing recognition by many clinicians of the first order of an unmistakable influence by certain of these organs on various fatal diseases, including some encountered during the present war, how could we hasten progress?
As an example submitted below will show, comparative analysis of coordinated data, i.e., garnering of all available data on a given subject, then arranging these data in logical order and sequence, will not only meet the first requirement, but point to the labors required to complete the work necessary to attain a satisfactory conclusion concerning the identity of a function. Various theories may be suggested by the coordinated data when carefully tabulated; a sound working hypothesis will soon assert itself by the wealth of facts from various directions for which it will afford a ready nidus, while wrong theories will soon meet their doom through lack of corroborative testimony, direct and indirect, and through its inability to find a logical place anywhere.

Purely to illustrate the workings of such a plan— which I have now followed myself, as far as private means could permit, for many years— I will submit a brief review of the present status of the prevailing views concerning the functions of the adrenals, and compare it with the totally different aspect of the question which the plan advocated offers.

In the April, 1917, number of "Endocrinology," you doubtless read the original article written by our fellow member, Prof. Swale Vincent, of Winnepeg, on recent views as to the functions of the adrenal bodies. Among the features reviewed is the discovery of Oliver and Schaefer in the early nineties, to the effect that "the function of the adrenal (or, at least, of its medullary portion) is to help to maintain the normal blood-pressure and to sustain the tone of the tissues innervated by the sympathetic system." You will also recall the experimental data which he adduces to show that Schaefer’s view is no longer ten-
able. Those of Young and Lehmann are quoted to show that ligation of the adrenal veins during thirty minutes, to dam back the adrenal secretion into the organs, and then allowing, on release of the ligature, the accumulated secretion to flow into the circulation, failed to evoke the expected result. Very little if any fall of blood-pressure followed ligation of the adrenal veins. "In fact," writes Vincent, "the experiments merely show that adrenin is poured out into the adrenal veins." Similar experiments carried out by Young, but with the adrenal veins tied several hours to exclude the adrenals totally from the circulation, gave similar results, there being no appreciable fall of pressure. Even removal of the adrenals by Austmann and Halliday, with concomitant observation of the blood-pressure, until the animal died, failed to affect the pressure curve more than would have ether administered as long as possible. The older experiments of Moore and Purinton, and the more recent observations of Hoskins and McClure—to which many others might be added—are quoted to show that inasmuch as very small doses of adrenin will lower the blood-pressure, the amount of adrenal secretion poured out into the adrenal veins would tend to keep the blood-pressure down rather than up. Briefly, the one great function upon which the practitioner has depended twenty-six years, the blood-pressure theory, should now be abandoned.

Virtually the same conclusion is reached concerning the second theory which has attracted some attention, the so-called antitoxic theory of Abelous and Langlois, in virtue of which the toxic effects of certain substances are neutralized by a substance elaborated by the adrenals. While referring to a few
isolated records which seem to favor it, Vincent states that "it must be confessed that the antitoxic theory has not been substantiated." On the whole, a few minor suggestions concerning possible functions, including the emotional stress theory of Cannon and de la Paz, and a summary of what he deems to be the state of our knowledge concerning the adrenal bodies, seem fully to substantiate Vincent's remarks early in the article that "we know nothing of the functions of the adrenal body regarded as an organ on its own account."

And the adrenals are not alone in this plight. The functions of the thyroid, parathyroids, thymus, pituitary, pineal and other organs of the series, are likewise well known to be obscure. One and all, viewed from the standpoint of prevailing teachings, stand in the light of another of Vincent's remarks concerning the adrenals: "There is no good evidence of an experimental or clinical nature which warrants us in believing that the adrenal body as a whole has any definite function."

Need we wonder under these circumstances that so erudite and conscientious a surgeon as Prof. W. S. Halsted, of Johns Hopkins, should be driven to write three years ago, after an attempt to elucidate the frequently fatal form of Graves's disease in which the thymus complicates the morbid process: "It must be evident to everyone that there reigns the greatest confusion on the subject of the functions of the glands of internal secretions"?

Gentlemen, it is difficult to conceive how all the work done since Oliver and Schaefer published their first paper on the influence of adrenal extracts on the blood-pressure, twenty-four years ago—or indeed.
COORDINATED DATA, ADRENALS

since Brown-Séquard published his initial dissertation on the adrenals over sixty years ago—can thus have proven futile. My own belief is that such is not the case. Comparative analysis of coordinated physiological and clinical data tend not only to sustain this opinion, but also to suggest that the adrenals may carry on a function of major importance—a function, moreover, capable of accounting for and including, as fragmental expressions of that function, what roles both physiologists and clinicians have attributed to the organ and sustained by considerable evidence.

The main features which led me to submit what might be termed the “respiration theory” fifteen years ago, and which much of the evidence recorded herein, has sustained since then, may be said to have rested upon five main conditions: (1) Addison’s disease; (2) adrenal lesions in acute diseases; (3) certain adrenal tumors, such as hypernephroma; (4) large adrenal grafts; (5) the unsettled state of physiological knowledge concerning respiration and metabolism.

As to Addison’s disease, the older contention that the adrenals were not always diseased, and that we were therefore dealing with a neurosis, is no longer tenable. Inasmuch as the disease has been shown to affect any part of the chromaffine system, including its ganglia, it is to disorders of that system that we must attribute the Addisonian syndrome, the leading or salient symptoms of which are progressive asthenia, weak heart action, vascular hypotension, emaciation, hypothermia, dyspnoea, vomiting, diarrhea, and, only in cases of sufficient duration, bronzing.
In the course of certain infections, diphtheria, scarlatina, malignant endocarditis, typhoid fever, pneumonia, etc., and particularly towards the close of these diseases, symptoms are observed which correspond with those of Addison's disease, viz., extreme asthenia, low blood-pressure, hypothermia, rapid breathing, cyanosis, weak pulse, tendency to syncope and heart failure. The post-mortem adrenal lesions in such cases vary from marked reduction of the residual adrenin and disappearance of chromaffin reaction, with cellular atrophy, to more or less marked interstitial hemorrhages, attaining in some cases the degree of adrenal apoplexy with sudden death. Among the recently described cases of this class may be mentioned those of Josué (2), Goormaghtigh (3), and Moltschanow (4). Excessive exertion in soldiers suffering from malaria, as often noted during the present war by Paisseau and Lemaire (5), or dysentery, as observed by Remlinger and Dumas (6) and Steiger (7), may also bring about adrenal lesions and in some instances adrenal apoplexy. Burns, according to Kolisko (8), may likewise produce this form of hypoadrenia. As I have been able personally to verify, 8 to 12 minim doses of adrenalin given hypodermically, in small quantities of saline solution, are positively life-saving in uncomplicated toxemias.

Hypernephroma, a form of tumor shown by Grawitz, in 1883, to develop from adrenal tissue, either in the adrenals themselves or in the kidneys, vascular walls and other tissues, may be composed of either or both cortical and chromaffin substance, though often merged with other neoplasms, cysts, papilloma, etc. When it occurs between the first and eighth year, as is often the case in the true adrenal
type, it may give rise to abnormally rapid body growth. In a case reported by Owen Richards (9) in a girl of seven years, the development was that of a woman of twenty. Such cases may show marked muscular development and strength. Parhon and Golstein (10) refer to a boy who, between the ages of 9 and 14, attained the size of a "vigorous man." Jump, Beatys, Jr., and Wayne Babcock (11) refer to a case of theirs in a girl of seven years, as "remarkably strong." This overdevelopment, however, shows none of the characteristics of acromegaly. Common to this type also is premature sexual development with profuse hirsuties, swarthy skin, etc. There is, as a rule, excessive appetite and thirst; gastric disorders and stubborn vomiting are sometimes observed.

The fourth feature was suggested by the fatal effects of large adrenal grafts. Bra (12), after grafting the adrenals of a dog into the cellular tissue of a child, witnessed its death in three days. Jaboulay (13) lost two cases, within twenty-four hours, after the same procedure. Courmont (14), in reporting a fourth case which likewise died in twenty-four hours, refers to the presence of "a formidable hyperthermia and cardiac collapse" while specifying that there was no infection of the wound. Nor had any been observed in the previously reported cases.

If any clue could be obtained from these clinical conditions as regards the function of the adrenal bodies—or rather of the whole chromaffine system in the light of modern work—it seemed to be that they at least played some important role in (1) metabolism, as shown by their influence on nutrition and general development and (2) on respiration, as shown
by their influence on oxygenation and the respiratory mechanism.

This brings in the fifth and last feature: the unsettled state in physiological literature of the very questions in point.

Concerning respiration, the many facts recorded by physiologists of the rank of Bohr (15), Haldane and Lorrain Smith (16), Vaughan Harley (17), Henriques and others, have tended to show that the diffusion doctrine of respiration is not valid. Pembrey (18), after an impartial study of the question has expressed the view that "the body of evidence has been steadily increasing in favor of the secretory theory, especially as regards the absorption of oxygen." What is meant here by "secretory theory" is that, as expressed by Bohr and Henriques (19), the respiratory process, to account for experimental facts observed, requires, in the lungs, a substance "having greater avidity for oxygen than the blood itself," or as they define it, "a kind of internal secretion." It is this function which from my own viewpoint the adrenal secretion seemed to fulfill.

We shall see later, that this view, which I submitted in 1903 and 1907 and repeatedly since in numerous articles, urging its importance in the intelligent interpretation of many diseased states, has recently (1917) been sustained by the researches of a physiologist, M. L. Menten (20), of the University of Chicago, who writes in this connection: "The presence of adrenalin in the venous blood of the capillaries of the lungs undoubtedly induces changes which meet the conditions suggested by Bohr (21) as requisite for an alternative to the explanation of oxygen secretion, that is, adrenalin could act as a substance
altering the property of hemoglobin so as to give it a greater attraction for oxygen as it passes through the lung."

COORDINATED DATA IN SUPPORT OF THE RESPIRATION THEORY*

These, reduced to their simplest expression, may be divided into six fundamental functional links:

1. The adrenal secretion passes out by the adrenal veins then enters the inferior vena cava.

As to the formation of the secretion, Stoerk and Haberer (22) found that the chromaffine substance develops in the form of intracellular granules which, when sufficiently dense, diffuse out of the cells into the adjoining small vessels and appear in the adrenal venules as a yellowish brown, refractile, mucoid material which constitutes the secretion that passes to the adrenal veins. According to Elliott (23), the adrenals of a normal man should contain from 4 to 5 mgm. (1/15 to 1/12 grain) of adrenin, but fright, anesthesia, infectious diseases and cardiac failure and post-mortem changes may reduce considerably this amount.

The presence of the adrenal secretion in the blood of the adrenal veins is suggested by the following facts: Gottschau (24) traced hyaline granules (found subsequently to be their secretion) from the interior of the adrenals to their veins. This observation was confirmed and amplified by Manasse (25), Aulde (26), and Stilling (27). Pfaundler (28) traced the same granules from the interior of the organ along the adrenal veins to the vena cava itself.

*The name "respiration theory" has seemed to the writer better to denote the process described—pulmonary and cellular—than the "secretory theory," which has no specific meaning, or "oxidation theory," which implies destruction by oxidation of the adrenal product and renders unnecessary the study of any function, since a "destroyed" substance cannot logically be credited with a function.
It is doubtless the adrenal secretion which is carried by the blood of the vena cava, for when blood originating from the adrenals on its way to this great trunk was injected into animals by Cybulski and Scymonowicz (29), it produced the characteristic effects of adrenal extract. These results were confirmed by Biedl (30), Langlois (31), and Dreyer (32), Szymonowicz, Biedl, Dreyer, Salvioli, and Pizzolini (33) found, moreover, that such effects could not be obtained with venous blood obtained from other parts of the body.

2. The adrenal secretion inevitably reaches the pulmonary alveoli where a reducing secretion is required to account satisfactorily for the absorption of oxygen from the air.

That the blood of the inferior vena cava containing the adrenal secretion reaches the pulmonary alveoli by way of the right heart needs but to be recalled.

We have seen that the classic diffusion doctrine of respiration has been challenged by a number of prominent physiologists, beginning with Bohr in 1897, and that this investigator and Henriques had concluded that a kind of “internal secretion” . . . . “having greater avidity for oxygen than the blood itself” was necessary to explain the phenomena witnessed. Besides their own observations based mainly on aerotonometric studies may be mentioned those of Paul Bert (34), who showed experimentally that the absorption of oxygen by the pulmonary blood persisted even when the pressure of this gas was almost nil; of Müller, who found that a strangulated animal exhausted the air in its lungs of all its oxygen; of Setschenow and Holmgren (35), Zuntz (36) and
others, who found but traces of oxygen in the arterial blood of asphyxiated animals.

3. The adrenal secretion has affinity for oxygen, reaches the pulmonary alveoli and affects the oxygen exchange.

Vulpian (37) found that adrenal juice reduced iron perchloride and iodine. Cybulski (38) recorded a similar action on potassium permanganate. Langlois (39) noted that adrenal extract lost its reducing properties in vitro when oxidizing compounds were added. Battelli (40) found that adrenalin did not lose its properties when contact with air was prevented, while Abel (41), Takamine (42), and others deem this property a source of trouble in laboratories, the latter chemist specifying that adrenalin becomes oxidized by contact with the air. A. L. Menten (43), a physiologist, adduces experiments which enable her to conclude that adrenalin "does particularly affect the oxygen exchange in that organ"—the lung.

4. The adrenal secretion influences actively the respiratory phenomena, including the intake of O and the output of CO₂.

D. E. Jackson (44) found that adrenalin produced prompt dilatation of the bronchioles when these are contracted, wholly independently of any rise of blood-pressure. The immediate relief afforded by injections of adrenalin in asthmatic paroxysms, a treatment now resorted to in preference to any other, is probably due to this fact. Januschke and Pollak (45) noted that injections of adrenin in doses of 1/10 mg. (1/600 grain) caused an increase of the respiratory excursions of the lungs. Though noticeable in normal individuals it was especially marked in animals suffering from muscarin asthma. Nice,
Rock and Courtright (46) found that whether adrenin were injected in minute doses, causing a fall of blood-pressure or in large doses causing a rise of blood-pressure, it evoked an increase in the depth of the respiration. Byelaventz (47) found experimentally that adrenin increased the gaseous interchanges. Bernstein and Faltz (48) observed that injections of adrenin in doses of 1 mg. (1/60 grain) subcutaneously, in normal individuals produced an increased consumption of oxygen and, conversely, an increased excretion of carbonic acid. The respiratory quotient was likewise increased.

5. **The adrenal secretion influences tissue oxidation.**

Adrenal extracts, as first shown by Oliver and Schaefer (49), cause a rise of temperature when injected subcutaneously in doses of 8.57 Grams of fresh gland, made into an aqueous extract, per kilogram of dog. Reichert (50) also recorded a rise of 1°C. in dogs, accompanied by increased metabolism from adrenalin in doses of 0.001 Gm. per kilo of body-weight. Morel (51) observed a rise of 0.9 to 1.8 F. (0.5 to 1°C.) in guinea pigs after rather large doses injected subcutaneously. Lépine (52) states that the increase of blood-pressure caused by adrenal extract in therapeutic doses is always followed by a rise of temperature. These observations seem controlled by the familiar facts that removal of the adrenals is followed by a steady decline of the temperature until death ensues.

6. **The adrenal secretion takes part in tissue oxidation and metabolism, by becoming a constituent of the hemoglobin.**
That the adrenal secretion can endow hemoglobin with its oxygen-carrying power, i.e., convert it into oxyhemoglobin, as I have repeatedly urged, has been confirmed by the observations of Menten and Crile (53), who noticed that the blood from the adrenal vein invariably assumed a bright red arterial color in from one to twenty minutes after dilution with salt solution, while blood from other organs treated in the same manner showed no change. This was found spectroscopically to be due to an increased formation of oxyhemoglobin. Menten (54) having added adrenalin to diluted human venous blood, found moreover, that it caused an increase in the intensity of the oxyhemoglobin absorption-bands (of which she gives photographs) and remarks that similarity between the spectra of adrenal vein blood and those obtained from venous blood to which adrenalin was added "is unquestionably very strong evidence that it is adrenalin which is responsible for the increased amount of oxyhemoglobin found in the adrenal vein blood."

RELATION TO OTHER THEORIES

The foregoing data, selected from labors of observers of recognized ability and standing, seem to suggest that the main disorders we, clinicians, attribute directly to the adrenals—the whole chromaffine system—are due, in so far as their symptomatic phenomena are concerned, to disturbances of that phase of metabolism and its corollary, nutrition, influenced by that system. Recalling the five clinical features which led up to this analysis, it would seem that Addison's disease and adrenal insufficiency due to infections may on good ground be attributed to deficient tissue oxidation, while typical adrenal hypernephro-
mata and large adrenal grafts produce their morbid effects through excessive oxidation.

True, various observers have not noted an appreciable alteration of protein metabolism in Addison's disease, but they lose sight of the clinical fact that the anorexia and inadequate assimilation of proteins may account for this. If, as observed by Senator (55) and others, the diet of these cases is increased and properly balanced, there is a notable gain. Particularly is this true if, as I have urged, adrenal gland or adrenalin is administered in judicious doses, i.e., doses adjusted to the blood-pressure and hypothermia, simultaneously. This coincides with the observation of Addis, Barnett and Shevky (56) that adrenalin administered subcutaneously in rabbits increases the urea excretion, provided the doses are not too small or too large. In the latter case, (as I have frequently observed in various nutritional disorders treated with adrenalin) cellular metabolism is interfered with by the undue constriction of the arterioles produced by the adrenal principle, and the resulting deficiency of arterial blood supplied to the cellular elements. Emaciation may thus be caused by its prolonged use by cases in which the disease present does not include emaciation in its pathology, bronchial asthma for instance. In one case, observed in consultation, the loss of weight exceeded thirty pounds. On the whole, there can be no doubt that the adrenal secretion influences metabolism.

This apparently applies likewise to the influence of adrenal products on the blood-pressure. There is no doubt that therapeutic doses raise the blood-pressure and that, as illustrated farther on in this paper, its continued use may induce a more or less perma-
nent rise of 50 mm. Hg. The clinic, therefore, supports the discovery of Oliver and Schaefer that adrenal extracts raise the blood-pressure. An increase of the rate of metabolism such as that induced by the adrenal principle also affects both smooth and skeletal muscles as also first observed by Oliver and Schaefer.

The antitoxic function attributed to the adrenals by Abelous and Langlois and others finds support in the fact that catabolism, that phase of metabolism in which tissue wastes, including the intermediate toxic wastes, are broken down, is partly due to oxidation. The conversion of these toxic wastes into eliminable end-products would then depend in a measure upon the integrity of the adrenals. Many clinical facts tend to sustain this view.

Finally, while the adrenal cortex, as much clinical evidence has shown, markedly influences both the sex characters and the premature development of sexual organs, hirsuties, etc., exaggerated oxidation, in which the organ in toto may take part, partly accounts for this morbid process, probably as a corollary to the specific role played by the cortex in the latter.

It would thus seem as if the adrenals through their dual action, specific and general, on metabolic activity were able to account for and explain the various "functions" that have been attributed to them. They all become, in the light of the foregoing, however, but fragmental expressions of a general function, thus justifying their authors for their deductions, though restricting them to their proper precincts.
It is purely as a clinician—and one indeed, always ready to accept gratefully any degree of enlightenment—that I submit the following analysis of the weak points of the respiration theory that might be urged against it.

The minute quantity of circulating adrenin fails to meet the needs of the respiration theory. Analysis of this question, if current teachings are taken as standard, suggests that the minimum concentrations given are not based on a sound foundation. Thus, according to Trendelenberg (57), this concentration is one part in one or two billions in the carotid blood of normal rabbits. Yet, we are taught by physiologists that adrenin is destroyed in arterial blood.

Again, we are told that it is by oxidation that adrenin is destroyed, while as we have seen, Abel, Takamine and others, found this property a source of trouble in laboratories. And yet no precaution seems discernible in the various procedures recited by the different authors who assayed blood to determine adrenin concentrations. Under these conditions it is very likely that at least a part of the adrenin is oxidized in the course of these procedures. Even the figures given for the adrenal veins are open to suspicion since, as shown by Menten (58), dilution of their blood caused an increase of oxyhemoglobin, which would entail a decrease of adrenin.

When the destructive effect of oxygen on adrenin is taken into account it seems also that there should be but one vascular area capable of affording a reliable assay, viz., the venous field comprising the adrenal veins, the vena cava, the right heart and pulmonary veins up to the air cells, where the blood be-
comes arterial. Once at the air cells, the adrenal product should be destroyed and remain so throughout all arterial channels and the whole venous tree (unless resupplied, so to say, in the subsidiary adrenal tissues) until the adrenals per se are again reached. The concentration in the adrenal veins is 1 part in one million, according to several investigators quoted by Barger (59). The venous channels between these veins and the air-cells being, of course, much larger, it is probable that Battelli’s concentration 1 part to 10 or 20 millions (60) is the correct one for caval blood i.e., one thousand times greater than Trendelenberg’s.

On the whole, the actual minuteness of circulating adrenin in arterial blood cannot justly be cited to controvert the many concordant data submitted in favor of the respiration theory.

The great quantity of adrenin needed to produce the effects recorded would kill by paralyzing the alimentary canal. The invalidity of this objection is emphasized by the teaching of physiologists that “adrenin circulating in the blood is rapidly destroyed” by oxidation. Such being the case the adrenal secretion would meet its doom on reaching the alveoli, thus preventing any action either on the stomach or intestines.

Abundant clinical experience also shows that such an action is not produced either when adrenalin or the adrenal gland are given by the mouth or adrenalin is injected hypodermically, endomuscularly or rectally during short or prolonged periods in therapeutic doses. This applies also to children. I could produce a large number of cases in which 3 to 7 minims given orally several weeks served only to act as tonic, and
to increase the appetite. In keeping with the observations of Loeper and Verpy (61), it often promoted the secretion of HCl where hypochlorydria existed. A medical patient suffering from asthma wrote recently, requesting my opinion concerning the continued use of adrenalin: “I have employed it for several months once a day, sometimes twice a day, hypodermically in doses of 10 minims of the 1-1000 solution.” His blood pressure rose from 130 to 180, he lost flesh and feared a permanent rise. Not a gastric symptom occurs, however, in the history of this case.

If inhibition of the rhythmic contractions of the intestine occurs in the lower animals, as shown by Ott, Magnus and others, even when injected in very low concentrations (1 to 20 millions, Magnus) (62), no appreciable effect of this sort is observable when adrenin is given in the therapeutic doses used in man. Possibly it occurs as an ephemeral effect of the constriction of the arterioles of the intestines similar to that caused by adrenalin throughout the body.

INVESTIGATIONS NEEDED TO DETERMINE THE VALIDITY OF THE OXIDATION THEORY

Some physiologists hold that the adrenals “in some way influence the metabolism of contractile tissues.” If the word “metabolism” is actually meant here, it would seem as if the word “destruction” (of the adrenal secretion in the blood) should be replaced by its conversion into something else that is not subject to destruction by oxidation. I have long held that it entered the hemoglobin, and endowed it with its power to become oxyhemoglobin; we have seen that Menten found that the adrenal product actually becomes converted into that body.
If then it does become converted into oxyhemoglobin, the adrenal secretion or principle must be taken up by the red corpuscles. Mulon (63) has found that the latter gave some of the reactions of adrenalin. Again, Traube, in 1853, concluded that hemoglobin could not fulfill the functions attributed to it without the aid of a catalyst, a substance capable of hoarding oxygen and crowding it, as it were, on the tissues as an "accelerator." Poehl (64) found that the adrenal principle was a catalyst, while Jolles (65) pointed out that the activity of a given volume of blood as a catalyst corresponded with the number of red corpuscles it contained. This suggests that the adrenal secretion (not necessarily adrenin, which does not represent the secretion in toto) is the corpuscular catalyst which supplies the tissues with oxygen.

In this connection, and possibly accounting for the small proportion of secretion produced excepting under stress, such as fright, excitement (Cannon), hard labor, disease, etc., its active principle may be an oxidizing enzyme—"adrenoxidase," as I once termed it. As Bayliss (66) states, "enzymes are merely a particular class of catalysts, considered for convenience apart, owing to the fact that they are produced by living organisms and are for the most part of unknown chemical composition." As an enzyme, adrenoxidase could act as an oxidizing catalyst without itself being destroyed. Now the oxidizing ferment of Bunge and Schmiedeberg (67), Jaquet (68), Abelous and Biarnés (69) and adrenin give heat reactions very similar to those of adrenin; while Menten (70) also refers to the influence of temperature on the activities of adrenin within fixed limits, a peculiarity of enzymes.
The adrenals or other chromaffine tissues would thus only be required to replace actual losses of the enzyme, the residual body asset of which would be conserved as the oxygen carrier and accelerator of the hemoglobin and constantly be re-used, while having lost its identity as adrenin. This would afford a legitimate nidus for the "function" suggested by MacMunn (71), who, having found haemochromogen in the adrenals, concluded that these organs served to break down worn out hemoglobin and histohaematinins. From my viewpoint, this process would serve to extract from them what constituents might serve for the elaboration of the adrenal secretory product.

Finally, much might be learned by trying to explain all the respiratory phenomena that have been attributed by as many physiologists and clinicians to adrenin in the foregoing pages to a function other than that of pulmonary and tissue respiration.

Need I urge in the presence of all these facts that a systematic cooperation between the physiologist and the clinician, each seeking to aid the other through the special knowledge he possesses, would greatly hasten our knowledge of the endocrine glands? Need I urge that all recorded data, physiological and clinical—of which the foregoing are but a few on the question treated—carefully tabulated and checked, then coordinated logically, irrespective of any preconceived theory, might open new fields which we would all, working in harmony, cultivate?

The respiration theory is only submitted here as one of the many fields of this kind. It may die a normal death; if it does, we shall at least have learned that the soil in that one area is sterile, and that another coordination of data of the many available...
may prove more fruitful. Many lines of thought may thus have to be dropped by the wayside, but the day must finally come when success will reward honest effort.

Of course, the coordination of all available data is no small task; but it is one to which I hope to devote my remaining days, with financial help the nucleus of which is available. All our members will be asked to criticize to their hearts’ content and to contribute from their store of observation or special knowledge, and if the true scientific spirit is shown in suggesting possible criticisms, our Association and its journal “Endocrinology,” will, I feel confident, prove a blessing to mankind in its far-reaching influence upon our knowledge of disease.

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