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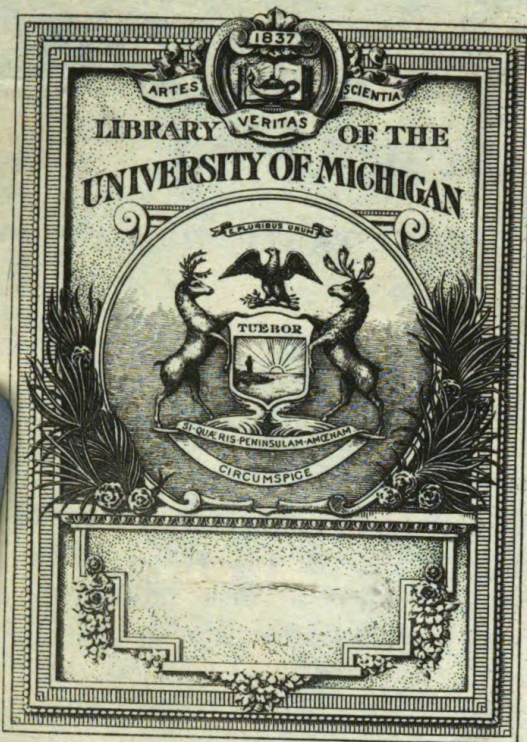
THE ADRENALS
IN
EVERY-DAY MEDICINE

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THE ADRENALS IN EVERYDAY MEDICINE

INTRODUCTION

1.—PRELIMINARY REMARKS

THE SUBJECT of adrenal insufficiency, or as it has come to be called, hypoadrenia, has been the basis for much clinical study and literary effort. There is also a good deal of misunderstanding about it, and as is the case with many medical problems, there are certain wide differences of opinion.

By way of introduction, it should be stated here in no uncertain terms that I am convinced that there is such a clinical entity as adrenal insufficiency aside from the well-known Addisonian syndrome which, of course, is now known to be the result of adrenal cellular destruction. I also believe that the adrenal glands are important factors in the maintenance of various responses of the body to various causes of diseases as well as in its normal physiological functioning.

An attempt will be made in the following pages to set forth the opinions of others, most of which are based upon clinical experiences, for hypoadrenia is essentially a clinical manifestation of far greater interest to the practitioner of medicine than to the laboratory experimentalist.

It is true that we are indebted to certain physiolo-

gists, among whom is Walter B. Cannon, of Harvard University, for much interesting information regarding the emergency function of the adrenal glands, and I am frank to say that my clinical experience has established my faith in Cannon's attitude and my disbelief of the criticisms of George N. Stewart, of Cleveland, who claims to have proved that at least a part of Cannon's experiences is but a house of cards.

From the standpoint of the general practitioner, I contend and expect to show by expressions of opinion by many others, that the adrenal glands deserve consideration much more frequently than heretofore has been the habit of the profession, and that the physiological therapeutic measure sometimes called "adrenal support"—a form of organotherapy the aim of which is to encourage and support the depleted adrenal system—is as rational a form of organotherapy as substitution therapy with thyroid extract in the cretin, or the case of myxedema.

Unfortunately, the rift between the clinicians and the experimentalists is quite a serious one, but I care not whether it is bridged or not, so long as the application of these fundamental ideas which I believe are thoroughly established from a clinical standpoint, renders a practical and clinically helpful service to those who see fit to study their patients from this standpoint and to apply this fundamental principle of homostimulative organotherapy.

It will be noted that a great many reports have been taken from foreign literature and that chief among the writers along these lines is Dr. Emile Sergent, physician to the famous Charité hospital of Paris, whose book, "Etudes Cliniques sur l'Insuffisance Sur-rénale (1898-1920)," is a remarkable collection of clinical papers. It indicates not merely that there is indeed much more to adrenal insufficiency than a "fetish," as Stewart has jocularly called it, but that

there is just as much ground for the attitude of Sergent and his colaborers as there is for Stewart and his friends, and that the following remark of Stewart is not founded upon well-balanced judgment based upon an extended clinical experience: "On the whole it must be granted that hitherto the attempts made to evoke in animals a well marked syndrome characteristic of adrenal deficiency have been singularly disappointing. The contrast is great when we leave this desert, where the physiologists and experimental pathologists have wandered, striking many rocks but finding few springs, and pass into the exuberant land of clinical endocrinology, flowing with blandest milk and honey almost suspiciously sweet."

The reader may judge this for himself and my personal advice to him is to suspend his judgment until he has definitely and repeatedly proved or disproved the numerous carefully worked out opinions which are collated in this Monograph.

2.—TERMINOLOGY

A few statements should be made regarding terminology. The term "adrenals" is shorter, lends itself more easily to adjectivization, and is used fully as often as the word "suprarenals."

The term "adrenin" is one that is used by most physiologists to represent the adrenal medullary hormone from a physiologist's or an experimentalist's standpoint. This same substance, however, when isolated and available in trade, for twenty years has been known as "adrenalin," though this term is a protected proprietary name.

If the word "adrenalin" is used, it should refer to the trade preparation. If, on the other hand, the medullary principle is mentioned, the trade name

should not be used, and here "adrenin" is the term.

Professor Abel, of Johns Hopkins University, apparently was running a race with Takamine, and the latter outstripped him, for more than twenty years ago (adrenalin was, I believe, first put out in 1902) when Abel made his announcement regarding epinephrin, it was found that this was not the actual active principle but one of the intermediary products very close to it—not quite the finished product—and shortly after this Aldrich and Takamine finished the race and called their product "adrenalin." Since that time, however, certain medico-literary authorities have seen fit to apply the term "epinephrin" to all adrenal medullary products, even going so far as to change the word "adrenalin" into "epinephrin" in abstracting articles about adrenalin. This, of course, is reprehensible.

Cannon prefers the term "adrenals" to "suprarenals;" he also, very properly, prefers the word "adrenin" to "epinephrin" or "adrenalin"—and I agree with him.

"Hypoadrenia" and "hyperadrenia" are natural developments of the word "adrenals." "Hypoepinephrinemia" is cumbersome and incorrect. "Hypo-adrenalinemia" is absurd, for one does not find the proprietary preparation, adrenalin, in insufficient degree in the blood or tissues.

"Hyposuprarenalism" is difficult and cumbersome, and so in the following pages we refer to the various substances and conditions as follows:

Adrenals: the suprarenal capsules, the adrenal glands.

Hypoadrenia: functional adrenal insufficiency.

Hyperadrenia: functional adrenal irritability or excess.

Adrenin: the adrenal medullary principle.

Adrenal gland (substance): total adrenal substance including cortex and medulla.

Adrenalin: the remedy made from the adrenal medulla.

Epinephrin: an intermediary product in the production of the adrenal medullary principle, adrenalin. Though now that the product patent on adrenalin has expired, several manufacturers have chosen to make imitations of adrenalin and call them epinephrin.

3.—ANATOMY AND PHYSIOLOGY

Anatomically, the adrenals “are two small, flattened bodies, of a yellowish color, situated at the back part of the abdomen, behind the peritoneum, and immediately above and in front of the upper end of each kidney; hence, one of their names, suprarenals.”

They vary in size from $1\frac{1}{4}$ inches to 2 inches (37 mm. to 60 mm.) in length, and are slightly less in width. Their thickness is from 2 to 3 lines (4 to 7 mm.) while their average weight is 60 to 90 grains (4 to 6 grams) each. They vary greatly in size, for they are “sometimes so small as to be scarcely detected.” Small accessory glands are often found in the cellular tissue that surrounds the adrenals, some of the larger of which have both a cortex and a medulla. The superior convex portion of the adrenal glands consists of the cortex, differing entirely in color, structure and function from the inner or concave surface lying adjacent to the upper end of the kidneys. This description of substances can best be verified by making a perpendicular section. The cortex comprises the greater part of the organ, is of a “deep yellow color, and consists chiefly of narrow columnar masses, standing perpendicularly to the surface.” The medullary substance, much smaller, is soft and pulpy, and of a very dark brown color. The arterial supply to the adrenals is rich and abundant. The nerves are very numerous and are

supplied from the solar and renal plexuses. The lymphatics terminate in the glands of the lumbar region.

Nearly seventy years ago (1856) the famous, though much-maligned, Brown-Séguard announced as the result of experiments which seemed to him quite conclusive, that a secretion produced by the adrenals is necessary to life in animals which were the subjects of his experiments, for all whose adrenals were extirpated had died, having manifested practically the same group of symptoms, which followed a similar course. Others repeated his experiments and failed to agree with his conclusions, since all their subjects did not die. Some experimenters since have denied the hormonal function of the adrenals, even charging the operator with a lack of manipulative skill, in order to throw doubt upon his conclusions.

A generation later these words were written and may be found in Kirk's Handbook of Physiology: "The failure to produce symptoms after attempted removal of the glands has probably resulted from incomplete removal, or the presence of accessory bodies." It will be remembered that accessory glands are not infrequently found in the periglandular connective structure, having both medullary and cortical tissues. Indeed, later observations seem to indicate that living, hormone-bearing masses of ganglionic tissue resembling that of the adrenals, and having similar physiological functions, may be found widely distributed throughout various portions of the body.

The dual structure of the adrenal glands and the decisive differences between the cortical and medullary cells have predicated a dual physiological function, and without a doubt these two dissimilar structures of different blastodermic origin are really different organs, just as the anterior and posterior lobes of the pituitary gland are different in form, structure and physiologic usefulness to the body.

It is believed that 85 per cent of the total adrenal substance may be considered as cortex, whereas the remaining 15 per cent, as though to make up for the small amount of this tissue, produces quite the most wonderful hormonal principle of which we have knowledge—the so-called adrenin—or, when available in trade, usually in 1:1000 solution—adrenalin. This crystalline, hormonal, organotherapeutic principle has been proved to be active in a dilution of as little as one to twenty million, and is not merely a physical wonder as a result of this, but a physiologic wonder as well.

4.—FUNCTIONS OF THE ADRENALS

About the middle of the nineteenth century two renowned physicians, Addison in England, and Brown-Séquard in France, gave us our first definite information concerning the functions of the adrenal glands, or suprarenal capsules, as they had previously been called in those few anatomies whose authors had thought it worth while to describe them.

The two writers named taught that the lives of vertebrates including the human family, are dependent upon these glands,—at least that their ablation, or total destruction by disease, was uniformly followed by death.

Little attention seems to have been paid to the functions of these organs in this country, but in Europe more or less study was given to them, and by the last decade of the century named certain investigators, Sergent, Bernard and perhaps others, wrote and described the syndrome of acute adrenal insufficiency.

In 1901 Takamine discovered adrenalin, the (now) well-known product of the medullary portion of these glands. If there are other substances produced by the medulla, we have not yet heard their names.

After Takamine made his notable discovery the spectacular feature of adrenalin as a vascular styptic seems to have caught the eye of a large majority of the profession and the drug adrenalin has enjoyed a popularity far in excess of the products of the cortical portion and, I believe, entirely out of proportion to its relative endocrine value.

While the large number of workers accepted the view generally held that since the cortical, or outer portion of the adrenals, was not so conspicuous by having been made into a product and enthusiastically offered as a therapeutic agent, it, the cortical hormone, might not be so valuable. Anyway, some investigators refused to have their minds clouded by the popular trend, but chose to do their own thinking. They persistently and continuously prescribed the product of total adrenal glands rather than only the adrenalin, a medullary product.

Quite recently certain physiologists—Gley and his coworkers in Europe, and Stewart, Swale Vincent and others in America—have sprung a surprise on the profession by publishing their laboratory findings with conclusions substantially as follows:

There is no physiological adrenalinemia (hyperadrenia).

From the researches of Gley and his coworkers (Camus, Porak, Quinquaud, etc.), he says that though adrenin is found in the adrenal veins, none at all is found in the suprahepatic veins. This, it is claimed, shows the rapid disappearance of adrenin in the blood, and Gley concludes, therefore, that adrenin in physiology or adrenalin in a therapeutic way, cannot exert a tonic action on the cardio-vascular system. Gley further declares, in substance, that unless the product of an endocrine gland can be found in the blood of the left heart, no claim should be made that it exerts any

physiological action on the organism. This being so, Gley continues:

“Does it not become difficult to preserve the syndromes of hypoadrenalinemia* and hyperadrenalinemia (such as they are presented) in the nosographic list where they have so readily taken such a prominent place? If adrenalin scarcely plays a physiological rôle, since it passes only exceptionally and in infinitesimal quantities into the blood of the general circulation, the so-called condition of hypoadrenalinemia does not correspond to a reality; the quantity of a fictitious product cannot diminish, and the disturbances which are said to be linked with this diminution are due, according to all the evidence, to another cause. Perhaps it would be proper to see whether a hypoadrenalism exists. At any rate, the insufficiencies of adrenal functioning, if they exist, do not seem to be dependent on a lessened secretion of adrenin.”

In his reply, published in *Presse Médicale*, Sergent says, in part:

“When, in 1899, I, with Leon Bernard, described the syndrome of acute adrenal insufficiency, adrenalin had not yet been discovered, and consequently I could not take into consideration the existence of clinical manifestations attributable to what Gley terms hypoadrenalinemia. To my mind, as well as that of my coworkers, the question was one of total adrenal insufficiency.”

A little later, following the quotation of a statement from Gley, Sergent continues:

“I think that this physiological interpretation is not irreconcilable with the facts proved by the clinic. Whether it be a poison produced by the gland, a trophic deviation (to employ Gley’s expression) or a hypo-functioning, it has nevertheless been established, that when the destruction of the gland is sufficiently exten-

* See “Remarks on Terminology,” Chapter 2.

sive, there results a clinical syndrome characterized by an aggregate of symptoms which are always identical, and that, at times—and this is the argument which is not without its value—can be ameliorated by total (adrenal) organotherapy.”

The adrenal secretions are physiologically unstable in their quantity of output from moment to moment and from hour to hour, in a higher degree, perhaps, than the secretion of any other endocrine gland.

Under the influence of an adrenal extract (medullary) injected into the veins or hypodermically, the cutaneous vessels are constricted, while the vessels in striped muscles are dilated; at the same time the effect on the heart muscles is that of a vasodilator, imparting greater power to the organ by the resultant increased blood-supply. Blood from the adrenal vein causes the same effects as adrenin (Cannon), or a laboratory-prepared adrenal extract.

When animals and men experience fear or rage or intense pain, these emotions call out a greatly increased quantity of adrenin which immediately exerts its influence in a manner suited to the occasion. By its influence on the unstriped muscles, particularly of the walls of the blood-vessels, it drives the blood from the abdominal organs (stomach, intestines, pancreas, spleen, etc.)—temporarily suspending their normal vegetative functions—to the vital organs, as the heart, lungs, central nervous system, and the voluntary muscles generally.

Adrenin, then, serves to mobilize the resources of the organism for the benefit of the organs and muscles most vitally concerned in combat, flight, or pursuit.

When this adrenal principle is introduced into the blood by injection (either by the intravenous or the hypodermic route), it causes the liver to liberate sugar into the blood stream. Reaching the cells, this sugar is promptly oxidized, stimulated thereto by the pan-

creatic internal secretion (Zuelzer), imparting added power to muscular contractions.

Adrenin relaxes the smooth (unstriated) muscles of the bronchioles, thus increasing the amount of air entering the lungs to augment the quantity of oxygen at exactly the time when greater power is demanded.

Glycosuria doubtless may be promoted in man and the lower animals by stimulation of the adrenals, through intense pain and the emotions. Through the same agency, also, great muscular exertion is accompanied by heightened blood-pressure. This doubtless follows in part, at least, from the constriction of the cutaneous and splanchnic blood-vessels, as already mentioned.

A few words further about the function of the adrenals in liberating sugar from the liver might be apropos. Cannon's extensive study and experiments along this line are of inestimable value. He says: "The injection of adrenin can liberate sugar from the liver to such an extent that glycosuria results. Does the adrenal secretion discharged in pain and strong and emotional excitement play a rôle in producing glycosuria under such conditions?"

"In clinical literature scattered suggestions are to be found that conditions giving rise to emotional states may be the occasion also of more or less permanent glycosuria."

It is well known that in 1913 Cannon and Fiske examined the urine of twenty-five members of the Harvard University football squad immediately after the final and most exciting game of the season, and found sugar in twelve cases. The intense emotions aroused by a contest of this sort, when thousands of spectators are ready to cheer or censure, release an extra supply of adrenin into the blood, and adrenin is one of the most potent means of tapping "the reservoirs of power." "The nervous impulses delivered to the muscles,

furthermore, operate upon organs well supplied with energy-yielding material and well fortified by rapidly circulating blood and by secreted adrenin, against quick loss of power because of accumulating waste." (Canon.)

This subject will be considered more at length in the chapter on "Diabetes and the Adrenals."

The simultaneous constriction of the blood-vessels over so vast an area as is here indicated, cannot fail to have a profound influence in heightening tension under the influence of pressure from the heart, the force from whose contractions is at the same time intensified, this organ being driven to more forceful activity by the self-same chemical agent—adrenin. This is equally true whether the influence of the adrenin on the muscles is direct or whether it is through the intervention of the sympathetic nervous system, as the experiences of some have seemed to show.

Repeated contractions of muscular tissue result in a loss of irritability to such an extent that they no longer respond to normal stimulation. By rest, this irritability is restored. Adrenin greatly facilitates this restoration, partly by improving the circulation, as has already been shown, but also by a specific antitoxic influence that it has been shown to exert upon the toxin in the muscle cells, so it appears that adrenin can restore normal irritability to a fatigued muscle in only a very few minutes as fully as rest could do it in several hours. (Bandler)

In a general way, Dr. Emile Sergent, physician to the Charity Hospital, Paris, defines adrenal insufficiency as "the suppression or diminution of the adrenal functions."

According to this well-known teacher and indefatigable worker, the adrenal glands have two functions, an antitoxic function and an angiotonic function. I will quote a few lines from his published works to

show his viewpoint regarding these functions, as follows:

“Under the term antitoxic function is to be understood the property which the adrenals possess of exerting a neutralizing power in respect to exogenous and endogenous poisons. Muscular labor engenders the production of toxic substances. The accumulation of these toxic substances—which is the cause of fatigue—when it is excessive, brings about physical overstrain, a veritably endogenous form of intoxication. The adrenal glands exert a truly specific, neutralizing action in respect to poisons of muscular origin, the effects of which are analogous to those of curare. Should these glands happen to be destroyed this neutralization is lacking and a condition of depression and muscular fatigue is seen to appear which, in man, we shall find in the form of the earlier symptoms of adrenal insufficiency—asthenia.

“These ideas are derived from the splendid researches of Brown-Séguard and particularly of Abelous and Langlois.”

Following the same author's line of discussion, it is known that pregnancy is a condition which is attended by virtual intoxication or toxemia. It is also known that during gestation the adrenal glands are both functionally overactive and even hypertrophied. This, then, must be another form of endogenous toxemia habitually combated in a similar manner by the adrenal glands. (Guieysse)

In the consideration of exogenous poisons, the antitoxic power of these glands seems not to be so readily demonstrated, yet Langlois and Oppenheim have stated, as reported by Sergent, that the “toxicity of atropin, nicotin, strychnin, also of phosphorus, arsenic and the urinary poisons, when mixed with a trituration of the adrenal glands, are observed to be less toxic.”

To quote further from Sergent:

"The angiotonic function is comprised in the rôle of the adrenals in the regulatory mechanism of the arterial tension. The investigations made by Oliver and Schaefer and Cybulski, established in fact, first of all, that by injecting adrenal extract into the blood of an animal a rise of the arterial tension is obtained."

Sergent also says that, "To one who knows the adrenal functions, the syndrome of adrenal insufficiency in man can readily be arrived at much more easily than that of experimental adrenal insufficiency. . . . And there again we have the proof that the clinic is not always restricted merely to the application of the data of physiology or other biological sciences, but that it is very often able to throw light on their obscure phases, complete their discoveries, and even precede them in the search for scientific truth."

To recapitulate: Several years ago (1917) Roger, reviewing the multiple functions of the adrenals, demonstrated, in part, by his own research, and that of his French colleagues, the rapidity with which the glands respond to different forms of excitation. Briefly, according to the results of his experiments, the adrenals restore the balance in the blood-pressure. This is effected almost instantaneously. Or, in other words, they at least counteract the power or effect of morbid factors which depress it.

Their influence intervenes in psychic disturbances as well as in material lesions of the nerve centers. Exhaustion of the heart induced by fatigue is combated by the adrenals, and they also modify the action of the pneumogastric on the heart.

They regulate nutritional metabolism and have some subtle and decided influence upon the consumption of sugar.

Still further, they aid in the elaboration of pigments,

of cholesterol and lipoids, and act also directly as well as indirectly (through the circulation) on poisons either found in or introduced into the organism.

It is easy to conclude, therefore, that having such a multiplicity of functions, the adrenal glands are, on the other hand, responsible for a multiplicity of disturbances.

Thus, it seems that the adrenal system is Nature's stabilizer of emotional disturbances; it serves as a "brake" in certain conditions, and a regulator in others. It is the little, potent peacemaker in the organism itself, and a vigorous opposer of outside sources of trouble, without which intervention, death rapidly will ensue.

II

THE ETIOLOGY

5.—EMOTIONAL CAUSES OF ADRENAL DEPLETION

PROMINENT among the factors responsible for a condition of adrenal insufficiency, is the emotional element. It is now understood that those mental and temperamental factors which act upon and through the sympathetic nervous system also influence the adrenals; and that the sympathetic manifestations resulting from pain, rage, fear, hunger and the emotions cause a decided stimulation of the adrenals, with an immediate production of a greatly augmented supply of adrenin to the circulating blood. This is followed, at a shorter or longer period, by an equally well-defined adrenal depletion or hypoadrenia. If this reaction is serious, and its seriousness depends on the character and persistence of the stimulation, it is likely to be accompanied by just such clinical manifestations as we expect to find in shock—vasomotor irritability and instability, hypotension, insomnia, depression, and an extremely well marked asthenia. This last symptom is the typical accompaniment of adrenal disease (Addison), and almost invariably complicates the syndrome of pluriglandular insufficiency.

This condition of hypoadrenia is not uncommon in consulting work, and complicates many more cases than one might expect. Crile's "anoci-association" is

nothing more nor less than an attempt to forestall just such a condition by the removal as far as possible of circumstances known to cause adrenal excitation prior to operation. Sajous has long emphasized the importance of "terminal hypoadrenia," while Sergent, of Paris, has written many an article upon "l'insuffisance surrénale." These contributions more than convince one that this endocrine syndrome is of quite common occurrence. This condition of hypoadrenia was an outstanding factor in the "vivisection of a nation," so well explained by Crile during his service in France, and which will be considered more in detail in the chapter "War Adrenal Insufficiency."

Elliot Smith, of Manchester, considers mental instability a common groundwork for the superimposition of adrenal insufficiency. His position may be summed up in his own words: "The real trauma is psychical, not physical." Rénon, of Paris, finds that neuropathic or arthropathic physical substratum is common in individuals subject to the more marked effects of "war shock."

Emotional disturbance, as an important etiological factor in producing adrenal insufficiency, has been given detailed and careful study by Walter B. Cannon, of Harvard. This influence of the emotions is succinctly described by the *New York Medical Journal* in a review of Dr. Cannon's monumental work, "Bodily Changes in Pain, Hunger, Fear and Rage."

"It furnishes basic facts for the specialized worker in psychology and medicine and it introduces the lay reader to the interplay of facts between the body and mind in a manner to fascinate him with these marvels of science.

"The author begins from the more obvious interrelationship of physiological activity with the emotional life as observed in the processes of digestion. He then proceeds to the neurological distribution, anatomical

and functional, which makes this possible. He shows that this makes possible also more obscure processes by which the glands of internal secretion, under similar control, are made accessible to emotional stimulus. Thus emotion may regulate or interfere with bodily changes which are essential in carrying out the organic needs of the body. Important among these are the liberation and distribution of blood sugar, the restoration of fatigued muscle, production of greater coagulability in the blood—all of which are proved to be closely related to the secretion of adrenalin. This in turn is also closely associated with emotional stimulus.”

Some time ago, J. S. Corbett, of Minneapolis, reported a series of experiments on animals that were reduced to traumatic shock by the usual methods. The final appearance of the animals was that of complete shock—muscular relaxation, pale mucous membranes, low blood-pressure and mental apathy, evidenced by unconsciousness with no ether. The adrenin content was 8 per cent and the average blood-pressure was 12. Six hours was the average time required to produce complete shock; but, in the animals in which the adrenal glands had been extirpated, it took only 1.3 hours of traumatization to bring about the same result. And further, those animals in which the adrenin content had been reduced by sciatic stimulation, but in which shock had not become manifest, went very rapidly into shock after a few minutes of peritoneal trauma. It was found that symptoms of shock become extreme with advanced adrenal depletion.

Crile has this to say on the subject:

“The criteria for the objective study of the suprarenals are epinephrin (adrenin) output, the electric conductivity and the histologic picture. Elliott, Cannon and others have found an increased epinephrin output and a diminished epinephrin content in certain cases

of exhaustion, for example, in exhaustion due to inhalation anesthesia, to infections, and to emotion. Short found no notable diminution in the epinephrin content in shock; Bedford found no diminution of epinephrin output in shock; Mann dissociates the suprarenals from shock. In our laboratory we found cytologic changes in the suprarenals in exhaustion from any cause, including insomnia, these changes being more marked in the cortex than in the medulla."

Sometime ago, Meyer Solomon wrote a paper entitled "The Syndrome of Asthenia, of Mental Origin," and since the chief cause of asthenia is adrenal insufficiency, it should follow that any condition that produces asthenia, of course would bring about a coincident hypoadrenia. Solomon believes that—

"Acute emotionalism, of itself, especially if prolonged, may cause temporary periods of asthenia or fatigue, as not infrequently occurs after pronounced anger, fear, and similar depressing or exhaustly emotions."

Thus, prolonged worry, continual fright and shock such as are experienced in war-time, habitual ill-feeling, i.e., anger, unhappiness, result in a more or less constant state of adrenal depletion, and as we shall see later, involve the clinician in the study of the endocrine aspects of many a condition in which such emotional factors are uncovered in the clinical history.

6.—ACUTE INFECTIOUS DISEASES

In continental medical literature it has been stated again and again that the asthenias suffered by those having typhoid fever, diphtheria, scarlet fever and other infectious diseases are essentially the results of an adrenal exhaustion. This has been accepted by many as truth, and these impressions have been strengthened by the favorable results which have been

reported when adrenal therapy has been tried to combat it.

This asthenia is not the weakness resulting from overwork, but an exhaustion essentially muscular, which comes on suddenly, even when no work has been done, that the will of the sufferer cannot overcome and which is hardly or not at all relieved by rest. It is believed that the severe toxemias of these serious diseases are responsible for an overwork of the adrenals, resulting in their almost complete exhaustion. This is the time when the therapy known as adrenal homostimulation is able to demonstrate its wonderful power to control the situation.

Indeed, it has been shown that the oppressive, distressing asthenia that sometimes suddenly comes on even in incipient cases of tuberculosis is favorably influenced by suitably administering, over prolonged periods, products of the adrenal glands. It is not claimed that adrenal therapy is able directly to influence the infection, but while all rational hygienic measures are being practiced, adrenal therapy and alkaline salts, many times shown to be lacking in all tuberculous cases, sometimes called calcium starvation, together may so favorably influence cellular changes and faulty metabolism as to supplement the hygienic measures adopted.

There is another condition sometimes occurring during the progress of serious infectious diseases in which the adrenals themselves become the seat of a more or less acute infection. Addison's disease and acute inflammation of the adrenals, sometimes following scarlet fever, are examples to be cited.

As stated elsewhere, all asthenias are not of pure adrenal origin. Hypothyroidism sometimes presents a syndrome in which marked asthenia is prominent, and since hypothyroidism undoubtedly lessens in some degree the power of the cells to resist infection, there

are cases of thyro-adrenal asthenia. Indeed, in their antitoxemic rôle these two glands are synergistic toward each other, and since toxemia is one of the most frequent conditions to be met in general practice, those who overlook this in their prescriptions must needs meet some unnecessary failures.

As mentioned before, the adrenals themselves sometimes may become subjects of infection. It is quite possible that this happens more frequently than medical men have thought. There is now available some evidence that cholera has so high a percentage of mortality because in addition to intestinal infection, with its copious alvine dejections, the adrenals also become the seat of acute infection, and that the "algid stage" with its frightful asthenia, low blood-pressure and sub-normal temperature, is the direct result of anadrenia of the adrenals rather than of the intestinal infection alone, and that adrenalin given with a syringe or total extract is the best treatment yet found when properly combined with other indicated treatment (Naamé).

This same Dr. Naamé has had some experience with adrenal therapy in cholera. In an article published in May, 1921, he says:

"Struck by the similarity between the choleraic syndrome and that of adrenal insufficiency, I had occasion, in 1911, successfully to use adrenalin in cholera; E. Sergent and L. Bernard had, not long before this, described a choleraic type of hypoadrenia, and Sajous, the illustrious endocrinologist of whose conception I was not aware, had pointed out the identity of the symptoms of advanced cholera and those which the ablation of the adrenals produces; but, strange to say, without recommending the use of adrenalin, and concluding that the principal cause of death is due to the great viscosity of the plasma, inhibiting the circulation in the capillaries, and notably in those of the adrenals and of the hypophysis.

"This method was followed by Piovesanna (of Mestre) in 1912, and by Debalen (of Saigon) in 1913, who obtained excellent results.

"Demetrescu later brought experimental confirmation in favor of this therapy. . . .

"The use of adrenalin in opotherapy would appear to explain why anticholera vaccine acts preventively and remains without effect so far as a cure is concerned. This is due to the fact that in the first case, the adrenals are healthy, while, in the second, being impaired, their defective secretion no longer aids in the phagocytosis. I will add that the carriers of cholera germs tolerate the latter, or rather, treat them deferentially, very likely on account of the integrity of their adrenal glands.

"The great tolerance which cholera cases have for adrenalin gives rise to the supposition that the fight against cholera devolves upon the adrenals, as the intestine has no bactericidal property: on the contrary, from the experiments of I. Cantacuzene and A. Marie, it is seen that a watery extract from the small intestine of a guinea-pig, harmless of itself, and mixed with a non-deadly dose of cholera vibrio, when inoculated in the peritoneum of a new guinea-pig rapidly produces an acute cholera.

"On the other hand, according to A. Marie, adrenalin has the power of neutralizing the soluble toxins; moreover, Sajous writes that it is the glandular secretions, which, in the blood, favor the production of germicidal and antitoxic substances, and of phagocyte cells.

"To be sure, different organs are affected in cholera, but it is to an adrenal deficiency that the choleraic syndrome corresponds, and the adrenalin combats the latter in its entirety.

"This is what Violle says in this excellent book on 'Cholera.'

" 'In 1911, Naamé initiated a new therapy for chol-

era; he treated his patients with adrenalin, and obtained great success. Physicians, particularly in India and Italy, applied this method and were equally satisfied with it. To-day, this therapy has become classic. With massive intravenous injections of saline solutions, adrenalin is, at the present time, the most efficacious means with which to combat algid conditions.' ”

Nicola Pende, the Italian savant who has written quite extensively on the subject of endocrinology for medical journals, is also author of a book on the subject, now in its second edition.

Pende gives expression to the conviction that the syndromes of adrenal insufficiency are not all easy to recognize, since the diagnosis has been too often made at the postmortems. Perhaps we might add that in all probability, in this country where many people—relatives and friends—do not take kindly to autopsies, and considering the fact that disease of the adrenals has so often not been diagnosed until we were taught by means of postmortem examinations abroad, many cases of death supposed to be from other causes, really were the result of injury or destruction of the adrenal glands. There are assurances, however, from foreign fellow workers (Pende, Sergent, and others), that many cases who die of typhoid, scarlet fever, diphtheria and other infectious diseases showing marked prostration before death, really succumb to involvement of the adrenals, rather than to the original malady.

The influenza epidemic of 1918, to which attention will be called more fully in Chapter 10, offered one of the most unusual opportunities to investigate at autopsy the influence of this serious infection upon the adrenal structure. One of the most interesting reports which has come to me was told to me personally by Dr. Edwin Kime, of Indianapolis, who spoke of having done autopsies on over one hundred and fifty soldiers, all of

whom had died of influenza. The pathological anatomy of the adrenals was studied carefully and a generous percentage of cases showed obvious macroscopic changes while microscopically there were divergencies from the normal in every case.

Another writer, this time in Brazil, published a small monograph entitled "Da Insufficiencia Suprarenal na Grippe," in which he cites a number of autopsy findings showing that structural changes in the adrenal glands were quite common in individuals dying with grippe. In almost every case there were microscopical phenomena of congestion and occasionally this was visible to the naked eye, especially in the cortex, and of course inflammatory and edematous manifestations were often present with the accompanying leucocytic infiltration, slight hemorrhages and even foci of necrosis.

This Brazilian writer, in the same monograph, urges the importance of the adrenal aspects of influenza and insists that hypoadrenia almost invariably is present and that it is of decided importance as a fatal complicating factor. He emphasizes that in his experience the adrenal aspects of influenza were well worthy of the study that he gave them and his experience showed that when this condition is uncovered and treated in the less serious cases there was convincing evidence that an organotherapy opposed to hypoadrenia was and still is a sound therapeutic measure. We translate the following from this writer's communication:

"Of the reality of influenzal hypoadrenia, modern clinicians are fully convinced, for in the recent (1918) pandemic which attacked humanity as a whole and to which Rio de Janeiro paid such a heavy tribute, the profession was once again made aware of its importance."

And later, after referring to the paucity of informa-

tion on the subject, in American and European medical reviews, he quotes Professor Ricaldoni, of Montevideo, Uruguay, who asserts positively that "this adrenal insufficiency is inseparable from influenza itself" and who further affirms that "the adrenal insufficiency of influenza accordingly is more fundamentally significant than that which may appear in all or nearly all of the general infections and many forms of intoxications."

As might be expected, we are told by Pende that it is the incomplete or partial adrenal insufficiencies that are most frequently encountered in practice. We have been taught to look for them after influenza, infectious fevers, prolonged mental distress, in tuberculosis, syphilis, carcinoma, infection at childbirth, and many other conditions.

In his book these words are found confirming the opinions already stated:

"The most frequent causes, however, of acute hypoadrenia are the adrenal localization of some acute intoxications and infections—typhus, parathyroid, epidemic icterus, spirochetosis, malaria, infective nephritis, uremia (Frugoni, Oppenheim and Looper, Paiseau and Lemaire, Ticken Pari)—and the greater importance of this fact is in the genesis of chronic adrenal alterations with a syndrome of chronic hypoadrenia."

It is further stated by Pende that though apparent recovery from the acute attacks may take place under the influence of suitable organotherapy, organic changes in the adrenals, in that manner engendered, remain, and later under unfavorable health conditions may manifest their existence by recurrent asthenia and all its associated and related ills.

7.—DRUGS, ALCOHOL, COFFEE

Numerous references in the literature indicate that the adrenal glands are largely useful to the organism because of their responsiveness to toxic stimuli. It is their business to be stimulated by poisons and toxins in order that they may bring about certain circulatory and detoxicative reactions which are necessary to maintain health and to assist in eliminating from the organism the poisons which are irritating it. There is an adrenal aspect to every case of poisoning just as there is to every case of chronic focal infection or acute infectious disease.

This adrenal stimulation by means of these poisons is the chief cause of hypoadrenia or adrenal insufficiency. The continued stimulation of the adrenal glands by all sorts of stimuli, both of the nature already mentioned and those due to emotional causes, naturally wears out these glands, and they become depleted just as any other organs of the body are depleted by excessive stimulation.

I have previously called attention to the fallacy of administering strychnia as a tonic to those who have serious adrenal insufficiency. Strychnia is useful from a therapeutic standpoint in that it stimulates the adrenal glands. The muscular and nervous tone which is brought about by administering strychnia is thought to be due to goading the adrenals, and undoubtedly in occasional instances the adrenals may be benefited by such stimulation; but in real hypoadrenia where these glands have already been overstimulated and as a result are functionally played out, strychnia and other alkaloidal tonics are contraindicated because they merely stimulate an already depleted organ.

In 1920, G. N. Stewart and J. M. Rogoff, of Cleveland, Ohio, published an article entitled "The Action of Strychnin on the Output of Epinephrin from the

Suprarenals." These authors found that strychnin causes a marked increase in the output of the adrenal principle. This increase is not transient but lasts for a considerable time. It was clearly shown that doses of strychnin well within the therapeutic range which cause little or no exaggerated reflex irritability can produce a considerable augmentation in the rate of output of this adrenal principle. This phenomenon was best seen with smaller doses of the drug, and with its subcutaneous administration.

It is very clear that the adrenals are stimulated by poisons, and there is no doubt whatever that when the adrenals are already seriously depleted as a result of some toxic irritation of these glands that the dosage of strychnin ordinarily given stimulates them still more, and this is a detriment merely because the glands are almost at the end of their capacity to stand stimulation, and instead of irritation or stimulation, in the sense that strychnin acts, these glands should be supported. In other words, they should be given the right kind of food and the right kind of circumstances to enable them to recuperate. This, I believe, is very much more satisfactorily done by organotherapy than by strychnin, and therefore when there is adrenal depletion and it seems that the patient needs a good tonic, instead of using the well-tried strychnin, use the less well-tried adrenal support and see how very much more satisfactory it is.

Arsenic, mercury, morphin and any of the opium derivatives, act in the same manner as strychnin. When morphin, for instance, is taken from a person, hypoadrenia invariably ensues. These drugs stimulate the adrenals to hypersecretion. There is, of course, a limit to this stimulation and worn-out adrenals are the result of protracted use of any of these poisons.

Alcohol acts in very much the same way as drugs. In a paper read before the Societe de Therapeutique,

Paris, Rénon said that the symptom complex which he described as due to *l'angoisse de guerre* is almost typical of dysharmonism and especially that form in which hypoadrenia is well marked. Rénon finds that a neuropathic or arthropathic physical substratum is common in individuals subject to the more marked effects of "war shock," and that the use of alcohol is a pronounced predisposing factor.

Undoubtedly coffee is a stimulant, otherwise the users of it would not complain of headache and no "pep" if they miss their morning drink. And while it may be true that those who manufacture coffee substitutes may be unduly concerned in emphasizing the terrible evils from coffee and caffeine because of financial returns that may come to them, there is no denying the fact that caffeine, the alkaloidal principle of the coffee bean, is in the same category with strychnia and other alkaloidal tonics.

Without a question, the stimulus which comes from caffeine is the result of the adrenal glands working a little faster than heretofore. They have the additional job of disposing of this caffeine before they can be "through for the day"; and since the adrenals normally are stimulated by many factors including those already mentioned here, sometimes additional stimuli may not be the most advisable thing, especially in individuals who have the symptomatology of adrenal insufficiency. Without a doubt there are times when stimuli are advisable just as strychnia may be used with advantage in many instances and coffee may be a soothing, warming, stimulating drink to those who drink it; but in individuals whose adrenal glands have been overstimulated the continued use of from one to five grains of caffeine a day is a serious detriment. I have repeatedly had called to my attention experiences with adrenal support, in the manner in which I am interested, in individuals who continue to use coffee. They did not

get the results they were looking for from adrenal therapy because the adrenal support which is supposed to accrue was being neutralized by the adrenal depletion caused by the caffeine.

Experiments have proved repeatedly the clinical basis of these particular experiences and there is now no denying the fact that the continuous use of coffee is a physiological detriment. The coffee interests of the country call attention to the fact that coffee stimulates the vital centers and the brain cortex. They say that it favors deeper respiratory movements and increases the heart beat and urinary secretion, and all of this is perfectly true because of the fact emphasized before that the continued caffeine stimulates the adrenal glands to produce adrenin which is responsible for bringing about these very conditions.

III

CLINICAL MANIFESTATIONS

8.—ASTHENIA—FATIGUE

PRACTICALLY all individuals with overburdened systems—that is to say, the majority of cases of chronic disease, which are so very common—suffer from asthenia. In fact, asthenia is probably the commonest single symptom seen in medical practice. The so-called “fatigue syndrome”—in which the patient tires too easily and too early, in which not only is there muscular tiredness, but initiative is lost and mental capacity is dulled—is one of the most important manifestations in chronic toxemias.

The adrenal glands produce an internal secretion which is known to exert an amazing influence upon the circulation. Adrenin is believed to be an important factor in maintaining cellular tone and especially that of the unstriped muscles of the heart and intestines. Through the musculo-tonic influence on the circulatory mechanism it assists in keeping the blood-pressure up; and thus favors both oxidation and detoxication (and it has been shown that adrenin also has a direct influence upon oxidation besides its indirect effect through its control of circulatory efficiency). By this same musculo-tonic effect digestion and alimentary tone are maintained, hence, hypoadrenia favors a condition of atonicity of the alimentary musculature which, in turn, causes stasis and toxemia. Thus another vicious circle is established. This hormone, ad-

renin, has been shown to "control the sympathetic system" though some deny this by seeking to show that the reverse is the case. As a matter of fact, the influence of the adrenals over the sympathetic is reciprocal and mutual. They cannot well be separated.

If then, asthenia is the usual concomitant of hypoadrenia, and both cause and effect are so very common, what causes hypoadrenia? This can be answered in almost one word: TOXEMIA. Poisons of any kind, in the most minute dosage, have an immediate effect on these most sensitive of all the organs of the body. It is their business to respond to these influences, for if they do not do this, the increased circulation and augmented oxidation which become essential and which are brought about automatically as the body's greatest means of protection against disease, fail to take care of the toxemia. It is true that there are innumerable forms of toxemia, some toxins which are the usual wastes of the body cells, some which are unusual as the products of intestinal putrefaction, some which we ingest wilfully (as coffee) or accidentally, some which are produced by the aberrant activity of certain organs and especially the endocrine glands (for "too much or a good thing is a bad thing"), and, finally, some poisons which are automatically made in shock, emotional storm or the various mental states like fear, rage, worry and so forth. In other words, practically all forms of stimuli of the nature mentioned stimulate the adrenals. Too often the persistency of these stimuli is more than these little glands can bear, and they play out, so we have hypoadrenia and asthenia plus.

Asthenia is abnormal fatigue. It is either general or, more especially, motor or psychic. Motor asthenia is extremely commonplace, due to various causes—infectious, toxic or psychic. In fact, asthenia is the commonest symptom in medicine.

Among the motor asthenias of endocrine origin, the first to be recognized was the asthenia of Addison's disease. It is connected with a serious degree of adrenal insufficiency, and is accompanied by marked arterial hypotension. Certain asthenias allied with adrenal insufficiency, however, are not necessarily Addisonian. This fact is well known to-day. They are very common and usually, but not always, are accompanied by arterial hypotension. Their recognition and consequently their organotherapeutic treatment will, according to Tom Williams, of Washington, D. C., permit the cure of a large number of sick, ticketed as neurasthenics, cyclothymiacs, melancholics and even hypochondriacs.

Certain cases of arteriosclerosis with hypotension enter into this category. The interesting point is that they were often asthenics already at the beginning of their arteriosclerosis, while they still had hypertension. This asthenia of hypertensive arteriosclerotics existing from the beginning, is well understood to-day. Maurice de Fleury was among the first to show its frequency. In such cases there is often a disturbance of the adrenal function. After a period of years it can border on asthenia due to adrenal insufficiency, an insufficiency itself secondary to the old glandular hyperfunction and without the mechanical participation of cardiac insufficiency. I have encountered not a few such cases in the last ten years.

The majority of the endocrine muscular asthenias are adrenal in their origin, but there are others which may be thyroid, thymic, parathyroid, pituitary, gonad or pluriglandular. Many European endocrinologists have added their weight of authority to support these data.

The endocrine origin of a muscular asthenia having been recognized, the diagnosis is not complete. The cause must be determined. In the simple cases it is

sometimes an infection (a beginning tuberculosis, convalescence from grip or pneumonia, etc.) and in others it is an intoxication. In the more complicated cases it may be a vascular, nervous or psychic disturbance, under the subjection itself of a previous endocrine disorder. It is often like this in the "hyposphyxia" described by Professor Alfred of Paris, which is to be given further consideration elsewhere in this Monograph.

An important fact is that the asthenia may not be the result but the cause of an endocrine insufficiency. Henri Claude believes that this is the case in the paralytic myasthenia of Erb-Goldflam. According to him the endocrine glands are normal or rather increased in size, but they are functionally exhausted by a truly excessive effort. This is brought about by the entrance into the circulation of poisons of inconstant origin (but which he believes occasionally may arise from a disordered thymus) which affect the nerve and muscle cells. In the Erb-Goldflam syndrome the multiple insufficiency of the endocrine glands (hypocrinism) by functional exhaustion is, therefore, secondary, just as the disappearance of the spongiocytes in the adrenal cortex is secondary to an intense or prolonged muscular agitation.

Speaking plainly, asthenia is really another name for cellular intoxication—the muscles after work are tired because of the excess of intracellular wastes which have been produced in a quantity sufficient to overburden the usual means of elimination. The treatment naturally is rest or the removal of work and activity, during which time the poisons are carried away by the circulation and disposed of by the organism. Muscular asthenia may be due to an increased production of these toxins or a reduced capacity to carry them off as manufactured. Both causes are commonly associated and the latter is most important.

If the circulation is insufficient, i. e., if the blood-pressure is low and the "circulatory pep" is below par or, in other words, if the regulating mechanism which controls circulation, cardiac efficiency and blood-pressure, is insufficient, asthenia necessarily must result from the accumulation of the ordinary amounts of cellular wastes. This would be aggravated if in addition to this there is an augmented production of these products. It also happens that poor circulation causes poor oxidation, which in turn causes an accumulation of intracellular wastes. So we have a vicious circle, one condition aggravating the other and vice versa.

The tendency of the cell is to die. "Man begins to die as soon as he is born." This means that there is perpetual production of wastes, which if modified ever so slightly is going to cause trouble. And the initial manifestation of this kind of trouble is asthenia.

John J. McNulty, of New York City, recognizes the pluriglandular involvement in fatigue, for he says: "The present state of psychophysical fatigue seems, to our present understanding, to be largely the expression of lowered functioning of the endocrine chain of glands—the so-called autoprotective mechanism. . . .

Fatigue, as we see it to-day, is an expression of under or exhausted functioning of the so-called endocrine chain of glands or tissues; and the rational treatment of psychophysical fatigue is the employment of associated ductless gland substances as they seem to be physiologically associated in the living normal organism.

"With our present partial knowledge of the functioning of the endocrine chain of glands, it appears as though the suprarenals were the first to show signs of fatigue, for the simple reason that they seem to have most of the work to do in the autoprotective function; therefore, a small quantity of desiccated pig's suprarenals should form a part of the formula of

associated gland substance employed in the treatment of fatigue—psychophysical weariness. . . .

“Fatigue, psychophysical weariness, is a current condition that should be scientifically recognized and met with physiological therapy, for it is this functional state (fatigue) that, left unrecognized and unaided may glide by unperceived stages into a structural change with increased embarrassment of functioning. Physiological therapeutics, understood in the fuller and more complete aspect, is the efficacious treatment of fatigue—psychophysical exhaustion. Present day sub-efficiency, disinclination, is but an expression of endocrine asthenia—tired functioning of the suprarenals and physiologically allied ductless glands.”

The fatigue that is refreshed by a night's rest is not asthenia, although the adrenal glands needs must be somewhat depleted after the vicissitudes of a hard day's work. So are the muscles tired for that matter, and the brain, and the other organs. But the fatigue syndrome, chronic fatigue, is the syndrome which is pathognomonic of adrenal depletion asthenia. Then, too, those individuals who are “born tired” are without question suffering from adrenal exhaustion and there may be more than a grain of truth in that statement that they were born tired, for the fatigue may be due to some congenital defect in their “physiological substratum.”

9.—POSTINFLUENZAL ASTHENIA

During the influenza epidemic of 1918, a few empiricists, like myself, suggested that there was an adrenal aspect to influenza and that adrenal medication would be in order. This idea, of course, met with considerable criticism on the part of the more conservative. There were physicians, though, driven to desperation, who saw light in the suggestion and were willing to

try adrenal therapy, even though some might call it "a shot in the dark." These men who had the temerity to accept the suggestions of such as myself, met with most decided success.

Gradually, though, information is being accumulated and published in the literature which gives a more stable aspect to those early empirical statements. A paper was published in July, 1919, by Cowie and Beaven, of the University of Michigan, telling of the clinical evidence in the involvement of the adrenals in influenza and influenza-pneumonia. A few points from their paper, which is based upon an extended clinical, as well as pathological study of many cases, deserve emphasis and it is a pleasure to be able to pass along this information.

The possible existence of disturbed function of the adrenal glands as a cause of the asthenia present in all cases of influenza during the course of the disease and during convalescence led Cowie and Beaven to make an experimental investigation. The most common and most marked symptom of adrenal insufficiency is asthenia (prostration). Low blood-pressure, another cardinal symptom of adrenal insufficiency, has been commonly observed by clinicians as being characteristic of influenza and influenzal pneumonia. The authors endeavored to determine, on purely clinical grounds, if possible, whether a hypoadrenia could be shown to be at the bottom of the symptom group so much in the foreground of this disease. Necropsy revealed hypoplasia of the adrenals and evidence of adrenal dysfunction. The occurrence of dysadrenia in influenza and influenzal pneumonia may be regarded as indicated by the cardinal symptoms, the characteristic rise in blood-pressure following the prolonged administration of adrenal products and the prolonged blood-pressure curve following the administration of adrenalin. That an endocrine disturbance is present in influenza and

influenzal pneumonia is further suggested by prolonged blood sugar curve after injection of adrenalin. Hypoglycemia is not present in influenza and influenzal pneumonia as has been found to be the case in some diseases of endocrine origin.—(From *Jour. Am. Med. Assn.*, Aug. 2, 1919, p. 363.)

In May, 1920, there appeared an illuminating and comprehensive paper by Dr. Sajous, which deserves the respectful attention of the medical profession, for his years of study and his preëminence in this field give Sajous the right to speak with authority. Several outstanding paragraphs will be quoted from this article:

“Need I say that the therapeutics of the disease is unsatisfactory? Formerly the coal tars, the salicylates, and quinin were sheet anchors. Not only have they been discarded by most internists, owing to their tendency to promote cyanosis, but they have not been replaced by remedies enjoying the same confidence. About all that has stood the test of time, in fact, is the importance of absolute rest in bed. On the whole, it is apparent that we have come to a standstill with nothing promising in sight—an estimate which applies equally well to several of our most destructive diseases. This is due to the fact that, as I have long urged, the functions of the endocrines are overlooked in the pathogenesis of these diseases and in the defensive processes through which they are antagonized.

“In 1907 I urged that the Pfeiffer toxin, the only pathogenic agent considered at the time, caused influenza by inducing a more or less marked paresis of the sympathetic system, also termed, about that time, the chromaffin system, owing to the presence in its nerves and ganglia of suprarenal substance. This paresis, in turn, by causing relaxation of the arterioles, permitted an excess of blood to flood the structures to which they were distributed, thus causing congestion on all sides.

This explained the marked congestion and swelling of the nasal mucosa and coryza; the passive sinusitis causing the frontal headache; the conjunctival hyperemia with lacrymation and suffusion; the swelling and intense redness or vermilion hue of the tongue, oral cavity, pharynx, larynx, and bronchi; the cutaneous redness or erythematous blush and the supposed high fever.

“I say supposed high fever because a rise of peripheral temperature may occur without the presence of actual fever, owing to the fact that the normal internal temperature is considerably higher than the peripheral; in the liver and lungs, for instance, it is 106.5° F.; in the carotid artery 105.4° F., etc. When the peripheral arterioles are sufficiently relaxed to allow arterial blood to flow through the peripheral capillaries, it is the internal temperature of the blood, transferred mechanically to the surface, which conveys the false impression that fever exists. The familiar slow pulse, which shows no parallelism with the temperature of influenza *per se*, further emphasizes this fact. . . .

“The seriousness of the morbid process as a whole only becomes apparent, however, when we realize the vicious circle that the alveolar invasion initiates. The early elevated temperature, as I have pointed out, is not a true fever—the pulse, in fact, being slow—but instead, the result of relaxation of the arterioles. This relaxation now finds its explanation in the general asphyxia due to the alveolar invasion, the adrenals along with all other organs being functionally impaired through deficient oxygenation, the adrenal secretion, as is well known, sustaining the contractile tone of the arterioles. But this functional impairment of adrenal functions in itself lowers general oxygenation and metabolism in the light of a function I have attributed to the adrenals, and which has since been confirmed by

others: that of supplying to hemoglobin a catalytic enzyme which enables it to become converted into oxy-hemoglobin—the function, we know, which causes venous blood to become converted into arterial blood. Indeed, the fact observed by Pfeiffer that even boiling of the hemoglobin did not prevent entirely the development of the influenza colonies shows that it is an oxidizing enzyme (which alone can stand the boiling point) in the hemoglobin—the enzyme I have termed adrenoxidase that the Pfeiffer bacillus utilizes or destroys while developing its colonies in the alveoli.

“Ample clinical and pathological evidence is available showing that the adrenals are involved in the morbid process. Many French clinicians—Josué, Netter, Sergent, Rénon and Floreant, Voison and Benhamon, Renaud, Lesné, Wanner, Lyon and others, either to counteract the low blood-pressure or adrenal insufficiency, used adrenalin, obtaining good effects. The Swiss internist, Eichhorst, also obtained excellent results with it, his mortality in two thousand, four hundred and eleven cases having been but fourteen: i. e., less than six tenths of one per cent. In this country, Diner, using it when the blood-pressure was below 110, found it helpful, while Reilly reports good results from a combination including three grains of suprarenal gland. Conversely, Rood found both adrenalin and pituitary extract practically useless. Cowie and Beaven likewise found adrenalin useless, but having satisfied themselves that the prostration in influenza was not due, as generally believed, to cardiovascular disease, concluded that it was due to adrenal deficiency, having obtained a prolonged blood sugar curve after injecting adrenalin, and also after the ingestion of glucose. Seven autopsies also showed that hypoplasia and dysfunction of the adrenals were present. F. P. McNamara, alluding to the ninety-five autopsies by Professor Winternitz of Yale, writes that among ‘other

extrapulmonary lesions that were more or less constantly found were hemorrhages in the adrenal bodies.'

"Internal medication to enhance the autoprotective resources of the body would further decrease the chances of infection. The adrenals and the thyroid, owing to their powerful influence on oxidation, metabolism, and immunity, acting in conjunction with trypsin—Abderhalden's defensive ferment—all of which acting collectively, which I have (1903-1907) termed autoantitoxin, constitute our logical foundation for this purpose. Stimulation of these organs, to endow them with exceptional activity during an epidemic, and thus enhance the efficiency of the defensive reaction throughout the entire respiratory tract, is thus indicated. The adrenals are directly stimulated by strychnin. This fact, which I urged in 1903 and several times since, has recently been confirmed by Stewart and Rogoff, who found, after an elaborate pharmacological study that therapeutic doses of strychnin caused a marked and lasting increase in the production of the adrenal secretory product."

The importance of this information cannot be measured, for it must be remembered that adrenal insufficiency accompanies all toxic conditions. This means that there is a likelihood of adrenal depletion in the usual acute conditions which constitute such a large share of medical practice during the winter. A good clinical habit to form is to take the blood-pressure, and when one finds low blood-pressure and asthenia together in febrile or postfebrile cases, with the development of subnormal temperature and considerable reduction in the alimentary wastes (urea and total solids), to all the other indicated treatment—hygienic, dietetic and medicinal—add the measure which I have called "adrenal support."

10.—THE ADRENAL GLANDS IN PNEUMONIA

Pneumonia is beginning to be well known as more than a pneumococcic infection with severe toxemia. It is essentially a circulatory disturbance and as such the study of the factors calculated to influence the circulation and the use of remedies which control the work of the heart and blood vessels, are likely to produce more satisfactory results than the other treatment alone.

If one estimates the blood-pressure in a dozen or a hundred cases of pneumonia no matter whether well-advanced or in the "threatened pneumonia" stage, as a rule it will be 110 mm. or less—more than often, less. The blood-pressure is reduced. The heart is working overtime and its rate is excessive, a pulse of 120 or more is usual. The temperature is high.

There is no case of pneumonia in which the function of the adrenal system is not deranged. It is impossible for the sudden and extreme toxemia not unduly to stimulate these important glands, with an eventful hypoadrenia. This adrenal depletion is more serious than the preceding hyperadrenia, for when there is an excessive liberation of adrenin it is quickly oxidized and practically the only symptoms of the temporary adrenal excess are sympathetic irritability, cardiac excitability and a dry mouth and throat.

The hypoadrenia is now believed by many clinicians to be both the precursor and the cause of circulatory weakness, collapse and death; and it begins to manifest itself much earlier than one has been accustomed to think. The adrenals are overburdened in the earliest stages of pneumonia—even before it is clinically possible to make an absolute diagnosis of this disease.

Obviously the essence of good practice in the treatment of this protean disease is to attempt to forestall complications, and adrenal insufficiency is the compli-

cation which is most common, most serious and most often overlooked and ignored. To prevent adrenal depletion is not the easiest matter but, at least, it is indeed a step in advance to realize that there is such a thing, and to watch the pulse and arterial tension with vigilance. Supportive organotherapy is certainly worth while, either adrenal substance or a pluriglandular combination calculated to homostimulate "the adrenal system."

According to Sajous, the function of the adrenal and also the thyroid glands has a very great bearing upon pneumonia and other infections involving the respiratory apparatus in particular. Death, when caused by pneumonia, is due primarily to adrenal failure, the expression of which is "rapid lowering of the arterial tension, marked lividity, edema of the lungs and extreme asthenia." The mortality records, wherein the senile form of pneumonia predominates, harmonize with this view. And the reason that the senile succumb so easily to this disease is because the adrenals are depleted and subnormal. Adrenal support is a logical therapeutic measure in these cases.

11.—WAR ADRENAL INSUFFICIENCY

During and immediately following the Great War, thirty or forty papers and addresses appeared relating to clinical experiences with the use of adrenal substance and adrenalin in shell-shock, post-traumatic asthenia, collapse following antityphoid inoculation, hypoadrenia accompanying acute infectious diseases and, in general, emphasizing the importance of the adrenal functions in military medicine.

There is a great deal of practical helpfulness in some of the papers of Emile Sergent, of Paris, who for years has studied intensively the adrenal functions and,

since the beginning of the Great War, has been successfully applying his ideas in an extended way in military practice. For many years this writer has insisted that the adrenals played a much more important rôle than was admitted, and it is largely due to his efforts that our present knowledge and our clinical use of adrenal substance, has become established upon a solid and practicable basis.

Sergent has found innumerable opportunities to verify his previous opinions and experiences with the relation of the adrenals to various asthenic syndromes. His work at a base hospital in France confirms the frequency of acute hypoadrenia following toxic-infectious influences, hemorrhage or shock. He calls particular attention to the possibility of individuals having a latent tendency to adrenal insufficiency which, under the stress of some acute toxemia, is suddenly aggravated with serious results. He encountered such conditions almost daily in sick and wounded men from the front.

In cases of this kind collapse is more likely to supervene in typhoid, influenza, pneumonia or other acute infections. Sergent uses adrenal substance as a prophylactic remedy, and also many times has tided his patients over this dangerous phase with hypodermic or even intravenous injections of solution of adrenalin.

In that part of Dr. Sergent's book (*"Etudes Cliniques sur l'Insuffisance Surrénale, 1898-1920"*) which is devoted to war adrenal insufficiency, in a sub-chapter dealing with "the importance of the notion of adrenal insufficiency and the rôle of adrenal opotherapy in war medicine and surgery," the author brings out the fact that the clinical lessons of the war made an unusually valuable contribution to the history of adrenal insufficiency as an ordinary clinical entity as well as affording a complete corroboration of his ideas and former work along this line.

He says that from the outset of hostilities he had the idea that the war conditions, multiplying, as they would, the causes favoring the production of adrenal insufficiency, would afford an opportunity to check up on a large scale the researches which he had been carrying on since 1898. He states that he was able, as a matter of fact, from the inception of the campaign, both in his military functions in the medical service in Paris, where some 50,000 men were examined within a period of ten months, and in his military service at the Charité, or in the rooms of the military hospital at Le Vesinet, to assemble quite a number of observations which confirmed him in his opinion. He says:

“In my previous investigations I strove to establish the fact that adrenal insufficiency, principally in its acute manifestations, recognizes two great categories of causes: Either the adrenal glands, which have so far been healthy, are abruptly modified by acute lesions which are more or less massive or discrete, deep or superficial (grave forms of infection and poisoning, hemorrhage, etc.) or, the adrenal glands, which already have been affected by chronic lesions, superficial or partial (sclerosis, post-infectious chronic adrenalitis, degeneration, tuberculosis, etc.) carry out their function in a more or less precarious and erratic manner, which corresponds to what I have termed ‘acquired adrenal debility’; that if, in such subjects, there should arise an intercurrent cause requiring on the part of the adrenal function an especial physiological effort (additional work—overexertion, traumatism, infection, or even slight intoxication), the adrenal debility will instantly manifest itself by the appearance of formidable complications of acute adrenal insufficiency, the gravity of which is in flagrant disproportion to the apparent slight importance of the chance circumstance which has induced them.”

Sergent goes on to state that in the armies in the

field physical fatigue, overexertion, epidemics, food intoxication, traumatism (wounds, important operations) are the causes of this difficulty which are encountered most frequently. And too, the common call to the colors brings side by side with many men in full health, some who are more or less sickly, among whom it is not infrequent to find those whose adrenal function is weak. Each of these etiological conditions might furnish matter for special development.

In an epidemic of typhoid which he encountered, this writer was impressed with the important extent to which adrenal exhaustion participates in the typhoid process. During the course of this epidemic he lost many patients; those cases which he saw happened to be particularly severe. He had the satisfaction of curing a large number. Adrenalin was administered in subcutaneous and buccal injections, in very strong doses which he had so far not ventured to give to adults, i. e., 4 to 6 milligrams in 24 hours.

Another French writer, Satre, reported some experiences with acute hypoadrenia in his military work. He had seen it following antityphoid inoculation and urged adrenal gland feeding in all cases where the beginnings of this condition can be detected.

Still another paper, by Drs. Ramond and Francois, which appeared in the *Bull. et mém. Soc. méd. d. hôp. de Paris*, October 8, 1917, concerns itself with a study of the disturbances of the adrenals resulting from the exigencies of war. Translating a statement we read:

"This protracted war, demanding of all our fighting men a continual moral and physical tension, forces overexertion on all the organs, especially the adrenal glands. The literature already contains manifold examples of weakness (asthenia), low blood-pressure and (acute) dyspepsia from Addisonism and in various acute infectious diseases. All bear the clinical imprint

of hypoadrenia. It is probably also an important feature in the clinical picture of the gassed."

In their service in about four months they have seen no less than twenty-six cases of actual Addison's disease, all of which died save four, in which other factors, amenable to treatment with suitable gland feeding, were present.

In the same issue of the above journal Merklen draws attention to the frequency of hypothermia in military practice, especially in soldiers recovering from pneumonia or other acute illnesses. It is accompanied by extreme weakness and depression, and while this writer does not express himself decidedly as to the relationship of the adrenals to this condition, he mentions that it may be due to adrenal insufficiency. I confidently believe that it is, for in my own study of chronic hypoadrenia (in neurasthenia, pluriglandular insufficiency, etc.) low temperatures are extremely common, one case in particular having a temperature as low as 87 degrees F.

During 1918 Carles of Bordeaux encountered fifteen cases of what seemed to be Addison's disease, in men on active service, although it displayed a tendency to spontaneous subsidence, even in the worst cases. The symptoms were banished by a few weeks of rest, abstention from meat, and treatment with adrenal extract. Symptoms developed after exhausting fatigue, an infectious disease, or gassing. The most striking symptom was asthenia, which was more mental than physical. For months even the men were incapable of doing anything that required thought—reading, writing, or answering questions. Under adrenal treatment their improvement was rapid. Bronzing of the skin was perceptible in all the fifteen cases and the blood-pressure was low, although this is common among all the men at the front. These severe cases of adrenal depletion are seldom able to resume active

service, even after recovery, for their adrenals are so below par that any further strain is likely to rearouse the old trouble, with grave consequence.

Crile's remarkable article "The Vivisection of a Nation" takes up a scientific study of the kinetic systems of the Belgians as they were affected by the war. The adrenals, of course, are an important part of this system, and, consequently, we had in Belgium virtually a whole nation suffering from depleted adrenals. The diseases and conditions that follow in the wake of fear, anger, injury, worry, grief, homesickness, etc., are outlined by Crile.

Some time ago there appeared in *American Medicine* (December, 1915, p. 922) a reference to Naamé's work with cholera and dysentery to which attention already has been called in this Monograph. He believes that the adrenal element is quite the most important of all and that the so-called "algid stage" is nothing but an acute adrenal insufficiency. Reference is made here to Sergeant's war experiences with this same serious condition. Two cases of choleric diarrhea were brought to the military hospital completely collapsed with absolute asthenia. One had for a long time shown symptoms of "an abortive form of Addison's disease," the other had recurring attacks of asthenia dating from a very severe typhoid fever some years before. Both cases showed the typical white adrenal line, extreme hypotension, reduced temperature and a decided tendency to collapse at the slightest provocation. Both were given adrenal treatment and rallied promptly under it. Following this report of Naamé's and Sergeant's experiences appears this pertinent statement:

"Incidentally this information is of just as great practical value in general practice as it is in the special conditions due to war. Hypoadrenia is not infrequent in the daily routine work and its relation to the severe forms of infectious disease is of extreme importance."

The extensive literature of the recent medico-military practice, especially on the continent, has established conclusively that the exigencies of war play an important part by their influence upon adrenal functions. Many a physician was not aware of the importance of hypoadrenia until its reality was forced upon him during his army experiences. Those who had such opportunities and others who followed the reports had plenty of opportunity to verify the importance of the subject as a whole during the first great epidemic of influenza and now, despite criticism by some physiologists and others without real clinical experience, hypoadrenia is a definite clinical entity of common occurrence and real seriousness. The appreciation of this and the realization of the measures calculated to prevent it as well as to modify it, has been indeed a great advance in clinical practice.

12.—THE ADRENALS AND MALARIA

Usually, it is an overlooked fact that the severe toxemia which accompanies malaria, like the toxemia which accompanies influenza or foci of infection, or for that matter any other poisoning whether from alkaloidal poisons, internally produced poisons or the poisons of infective conditions, protozoal or bacterial, always have the same fundamental influence upon the adrenal glands.

Adrenal insufficiency is an invariable concomitant of malaria. The severe asthenia which follows the attacks, is, to my mind, just exactly the same proposition as that severe and persisting asthenia which has so uniformly followed influenza. Postmortem examinations of patients who have died of severe forms of malaria have been made in some foreign countries, but the same thing has been done in this country many

times in cases of influenza, and an army man in Indianapolis, who has published a very comprehensive report on the subject, assures us of the fact that the adrenal glands were obviously changed in a very large percentage of cases, and in the balance of the cases that had died of influenza, where there was no obvious change, there was a microscopic one.

That there is an important relation between malaria and the glands of internal secretion, is a claim made by a writer in the *Indian Medical Record* for December, 1920. This can be readily appreciated when one considers that these glands are the chief factors in the defensive mechanism of the body, and the part played by quinin in the treatment of malaria, for example, is merely to hold the protozoal infection in check until the resisting power of the patient can overcome them.

And according to an editorial writer in *Clinical Medicine*, it has been found that adrenal insufficiency accounts for the asthenia, cachexia and anemia so generally encountered in malaria. It is also responsible for the digestive disturbances that are frequent in the chronic form of the affection. It is only logical and reasonable, then, to prescribe adrenal therapy along with quinin in the treatment of severe forms of this disease.

Two French physicians, Paiseau and Lemaire, noticed a syndrome suggesting severe adrenal insufficiency in the course of three cases of pernicious malaria; viz., extremely low blood-pressure without changes in the heart rhythm, vomiting, diarrhea, lumbar and abdominal pains, extreme weakness and white dermographism. Autopsy revealed advanced degeneration of the adrenals and local hemorrhages, and in one case, foci of necrosis. The malarial parasite was found in the adrenal tissue. These authors believe that the adrenal syndrome occurs in malaria more often

than is generally recognized. They advise adrenal therapy even in the mildest stages of this disease when the symptoms suggest adrenal insufficiency.

While no one will deny the fact that quinin occupies an important place in the therapy of this disease, it is a specific for malaria. It is also an alkaloidal poison and there are detrimental results from the use of quinin just the same as there are excellent results from it, and as a matter of fact, quinin still further depletes the adrenals of individuals whose adrenal system is already in need of support, and thus the matter assumes quite an important aspect.

A report of three serious cases of malaria is made by a South American physician, Fraga. In each of these cases there was a syndrome of acute hypoadrenia present, and he believes that this was undoubtedly the result of the malarial toxemia. And, according to the same authority, the clinical importance of this form of malaria lies in the fact that adrenal therapy will tide the patient past the danger point. In what he terms "the algid form," intravenous injections of adrenalin solution "may complete the triumph of quinin." Fraga says though that in the less severe cases gland feeding alone may prove sufficient.

To my own way of thinking, hypoadrenia is present in *every* case of malaria, and is the essential foundation of the cause of the severe asthenia which prostrates the patient after the chill. Several years ago I put forward a theory regarding the adrenals in malaria which is yet to be discredited or proved. I believe that in one stage in the cycle of experiences in malaria there is a decided adrenal excitation, due to the sudden periodical liberation of the plasmodia and, of course, their toxins. One encounters the dry mouth as often as salivation, both manifestations of sympathetic stimulation. The heart action is always rapid and sometimes irregular. Then, as an aftermath of the

chill, we find the muscular relaxation, prostration, depression and asthenia, all of which are identical with the findings of severe adrenal insufficiency.

If there is an effort made early to forestall the expected adrenal "let-down" by suitable organotherapy, the severity of the weakness may be diminished and the possible development of such serious conditions as Fraga speaks of is minimized. This is exactly the broad procedure that is suggested repeatedly elsewhere, in influenza, alimentary toxemia, pneumonia, neurasthenia, etc. Render prophylactic adrenal support by suitable pluriglandular therapy, especially in individuals who at the outset show evidence of hypoadrenia.

13.—DIABETES

The problem of diabetes, its relation to the incretory organs and its treatment by organotherapy has caused the publication of a large number of articles both here and abroad. It is now an undisputed fact that the capacity of the body to burn up sugar is related to the glands of internal secretion. Disturbed thyroid function may cause glycosuria. We know that hypopituitarism causes a very marked increase in the tolerance to sugar, and also that the adrenal glands are very definitely related to glycosuria. It is for the last reason that diabetes is given consideration in this Monograph.

According to von Noorden, of Frankfort, there are two organs which control the sugar-forming processes to a considerable degree, and these act as antagonists to one another. He says:

"The pancreas is the first regulator to be considered. The blood from the pancreas passes to the liver and contains a specific product of the pancreatic cells (called an internal secretion), which exerts a retarding influence upon sugar production. If the pancreas

be removed from the body this influence is also removed, and the amount of sugar produced in the liver is greatly and irregularly increased. Each type of material from which sugar can be produced becomes grist to the mill, and enormous quantities of sugar pass into the blood stream and raise the sugar percentage to an abnormal height, while a large amount escapes from the body in the urine. This is practically a severe type of diabetes. Clinical experiences show that diminished activity of the pancreas is the cause of a large number of cases of diabetes. This altered power of the pancreas is chiefly one of weakened function; there are not always anatomical changes in the structure of the gland. There are all grades of pancreatic insufficiency, and, dependent upon the condition of the pancreas, the disturbance of the regulation of the sugar processes is either intense or slight. It may vary considerably from time to time in the same case.

“The other regulator is the suprarenal gland system. Minute quantities of adrenalin are being continually produced by this system and pass into the blood. This interesting substance possesses the property of exciting the sugar production in the liver to a high degree. As a rule the injection of about one milligram of adrenalin under the skin or into a vein will cause the excretion of sugar in the urine of an adult man within a quarter of an hour, which may continue for several hours.”

Von Noorden also says that experiments upon animals have shown that if there is a daily injection of adrenalin there is a regular response in the way of urinary sugar. The quantity, though, decreases until it finally disappears unless the dose of adrenalin is increased. This would indicate that the pancreas had built up an effective immunity or response to the abnormal stimuli.

“In the beginning, injections of adrenalin, or an increased function of the gland itself, both excite the liver markedly. The pancreas, surprised, as it were, at the vigor of the irritant, is not able at the moment to avert the danger; it has to allow the undue increase of sugar production to have its sway. After some days, however, the repeated stimulation forces the pancreas to throw off its inertia and to oppose the action of the adrenalin.”

This same writer says that the adrenals and the pancreas are not able to act entirely independently—that is, in their control of the sugar mechanism, and this is especially true of the adrenals, which are functionally and developmentally under the control of the nervous system—the sympathetic system acting as an intermediary between the central nervous system and the glands of internal secretion.

“The exact area of the nervous system which exercises this power is situated at the junction of the brain and the spinal cord. This well-known fact was discovered by Claude Bernard. The glycosuria which results from the puncture of Claude Bernard’s center in the medulla is due to the action of the central nervous system upon the suprarenal glands via the sympathetic nerves; adrenalin is at once formed in larger quantity, passes into the blood, and stimulates the sugar production in the liver. This ‘piqûre’ glycosuria is practically the same as suprarenal glycosuria.”

Louis Henry Levy, of New Haven, writing on diabetes in the *New York Medical Journal*, in 1915, also refers to the part that the adrenals play in this disease. He said:

“It has been found that pancreatectomized dogs develop glycosuria. It has also been shown that as much as four fifths of the pancreas may be removed before sugar appears in the urine. Simultaneous removal of both adrenals and the pancreas prevents the develop-

ment of glycosuria. This would tend to point to an interrelationship between the two glands. Injection of adrenalin into the system produces glycosuria. It has been found that with people and animals during periods of excitement sugar is often present in the urine. During these periods of excitement, an increased amount of adrenal substance is found in the blood. Hence it must be assumed that the glycosuria is due to the increased amount of adrenal substance. Normally this increase is held in check by the pancreas. However, when the pancreas is excised, or when the islands of Langerhans are involved in some pathological process, the check on the adrenals is removed and the liver is stimulated to an overproduction of sugar."

W. Langdon Brown, of London, regards diabetes as a product of an exaggerated metabolism evoked through the sympathetic. The thyroid, adrenals and pituitary are all overstimulated, but the pancreas is underactive. It may be due to a functional disturbance or to structural changes in the glands affected, and this increased metabolism asserts itself first in relation to the most abundant food material (carbohydrate), but later expresses itself in relation to all.

Koopman, of Holland, often has found that the adrenals were diseased in cases of diabetes. This relation has been noted by many investigators, among whom are Emil Weil and Plichet, K. Dresel, A. Ribot and Leon Binet.

Von Noorden has well named the pancreatic hormone—"the brake to the sugar factory." It is sometimes called the Langerhansian hormone, after the islets of Langerhans, in the tail of the pancreas. These islets produce the hormone which exerts a large control of the sugar mechanism. Lepine, of Lyons, calls it an anti-hormone, for indeed the chief function of the pancreatic internal secretion is not to "arouse or

set in motion" but to regulate the mobilization of sugar, a function which is activated by the adrenal principle to which the pancreatic hormone is the direct antagonist.

In other words, diabetes mellitus really is often a condition of pancreatic hormone insufficiency and essentially a deficiency of the tail of the pancreas, because ninety per cent of the islets of Langerhans are found in the posterior portion of this gland. Correspondingly, pancreatic diabetes, so-called, in part at least, is a condition of adrenal sensitization due to the removal of part or all of the antagonizing hormone influences of the pancreas; and it is very probable that the initial disturbances of the digestive functions of this gland are responsible for the development of the diabetes, for diabetes is essentially a disease of those with overworked digestive organs.

It is, then, a disease in which there is an uncontrolled adrenal function, and whether the adrenals are the active factors in the pathology of diabetes or not, certain it is that if the "brake" to the sugar mechanism is removed or not effective, the adrenal system must be looked to as at least one of the potent factors in the body which are speeding up the abnormal production of sugar. For this reason these little glands deserve serious consideration.

14.—FOCAL INFECTION, ULCER, ETC.

Hypoadrenia very commonly accompanies infective conditions and it seems to make little or no difference whether the infection is in the head, gall bladder, appendix, pelvis or elsewhere. The infective conditions so commonly encountered by the nose and throat surgeon, all have a more or less important adrenal aspect. There are many nose and throat surgeons who have

come to the conclusion that in addition to removing as best they can the foci of infection in the tonsils, sinuses, etc., the simultaneous support of the adrenal glands is a rational means of antagonizing the lassitude, asthenia and consequent neurasthenia which so often accompany conditions of this kind.

Focal infection, the most common cause of adrenal insufficiency, should be sought for most carefully, and every effort made to remove it. Many a neuritis of the arm is based upon several bad teeth. Or a tonsillar infection may occur in apparently normal tonsils, in which the crypts only are infected, and in which there is no obvious swelling or anatomical change.

The study of European literature reveals the rather surprising fact that gastric ulcer is considered by many investigators to be an endocrine disease and is amenable to ordinary organotherapeutic medication. The following is given to introduce this view of the subject and may serve in part, at least, to justify the claims of European investigators.

Dr. Teofilo Hernando, professor of the Faculty of Medicine of the University of Madrid, in his inaugural speech at the Bilbao Congress in Spain, dealt exhaustively with the subject of gastric changes of endocrine origin.

Speaking of adrenal insufficiency as related to gastric ulcer, he remarks:

"Our experience has enabled us to get together a certain amount of data which appear to demonstrate the existence of a relationship between both processes."

He says that contrary to what usually occurs in medicine, where, as a rule it is experimentation which verifies and amplifies clinical facts, in this case it is experimental data which has preceded the clinical observations. Cioffi, Gibelli, and Pende pointed out the frequency with which hemorrhagic erosions were encountered, and even real gastric ulcers in animals

which had died as a result of extirpation of the adrenal capsules. He recalls that Finzi was the first to accomplish a systematized work in that direction and that he concluded from his experiments on dogs and rabbits that adrenalectomy was followed by circulatory changes of the gastric mucous membrane—edema, hemorrhages, and processes incident to necrobiosis, etc. Where adrenalin was injected into a decapsulated animal, or an adrenal capsule of another animal was implanted, these lesions did not manifest themselves.

The writer later refers to eight cases observed by himself, as reported at the session of May 12, 1919, of the Academia Medico-quirurgica Espanola, "Insuficiencia suprarenal y ulcera gastrica." (Incidentally, one of the medical men attending that meeting related that he had that very day seen an Addisonian patient with gastric ulcer.) All these cases presented more or less marked symptoms of adrenal insufficiency, such as asthenia, pigmentation of the mouth and skin, and hypotension. In five there was bradycardia. In two, the examination of blood by Dr. Marañón revealed the presence of hypoglycemia.

Further on, we find the following:

"The lymphatic condition is also one of the characteristics of adrenal insufficiency, for, as we shall state hereafter, there appears to exist a real antagonism between the lymphatic system and the chromaffin. Thus, those suffering from adrenal insufficiency have an intense lymphocytosis (Neusser and Wiesel, also, Marañón, ourselves, etc.), and at the autopsies a great development of the lymphatic system is found. On the other hand, Wiesser and Hedinger proved there was a decrease of the chromaffin system in lymphatic subjects. Apart from the fact that this condition may create a predisposition for the development of adrenal insufficiency, there is not the least doubt but that the diminution in the chromaffin function induces a hyper-

plasia of the entire lymphatic system, as established by Pende, Growe, and Wislocki in their experimental studies."

And again:

"Those affected with adrenal insufficiency are usually vagotonic, as may be evidenced by submitting them to the pharmacologic tests and radiologic examination. We have observed, as have Gautrelet and Coureaud how violently these patients react to pilocarpin. After taking a milligram, or even half a milligram, they have an intense desire to evacuate, with sweating and intense salivation, all accompanied by a general discomfort which renders necessary the use of adrenalin or atropin, whereby the unpleasant situation is righted. The test for adrenalin glycosuria was always negative."

Continuing, Hernando says that, as already mentioned by him, this predominance of the vagus in adrenal insufficiency appears to be confirmed by the experimental studies made by Gautrelet and Thomas, as well as others recently carried out by Roger, of Paris, who observed an increase in the excitability of the vagus following capsulectomy, with this peculiarity, that upon injecting adrenalin into decapsulated animals they react in the same manner as normal animals to stimulation of the pneumogastric. All this, says the author, is easily explained, because the adrenal capsules secrete sympatheticotonic substances, and when the former disappear the tone of the sympathetic decreases while that of the vagus increases.

"We have already," writes Dr. Hernando, "alluded to the objections made by some physiologists to this conception of the part played by adrenalin. We also pointed out how, in their studies, Rogers and his followers show that the nucleoproteinic material contained by the gland is even more active than adrenalin, especially for the production of phenomena of gastric inhibition."

He says further that in cases of adrenal insufficiency there is another factor, seemingly important, in the production of vagotonia—the predominance of the lymphatic system. He quotes a number of authors in this connection, and then adds:

“It is evident, notwithstanding the confusion in our knowledge regarding the state of the vegetative nervous system, that in people affected with adrenal insufficiency a decrease of the stimulating substances of the sympathetic (chromaffin system) is met with and an increase of the substances which depress (lymphatic system). This creates an exchange of the gastric innervation, which may be attended by muscular spasms, followed by vasoconstriction, which facilitate the auto-digestive function of the mucous membrane. At all events, we would always have to reckon with a diminution in the function of the sympathetic (a change which no one questions in adrenal cases) and which would explain perfectly the ulcerous erosion, seeing that upon the integrity of that nerve are probably dependent the circulation, secretion, and sensibility of the stomach, which contribute so much to the maintenance of the life of the gastric cells.”

Recapitulating his entire paper, Hernando arrives at the following conclusions:

“1. The internal secretory glands exert their influence upon the digestive apparatus by two distinct mechanisms: by direct action of the products of their secretion upon the muscular fibres and digestive glands or through the intermediary of the nervous system of vegetative life.

“2. Every disease requires for its development a certain degree of predisposition; hence, a perfect organism ought to withstand the influence of all ordinary causes without being affected thereby,—a degree of resistance to which man, as now constituted, has not attained.

“3. Stiller’s asthenia (Glenard’s splanchnoptosis), a suitable ground for the development of many digestive complaints, may be regarded, together with other constitutional conditions, as a consequence of congenital alterations of the endocrine glands and of the nervous system, which are the two great regulators of all the phenomena of the organism.

“4. The changes in the functioning of the endocrine glands may be the cause of alterations in the secretion of gastric juice.

“5. Of these alterations, the hyposecretory types are more frequent than the hypersecretory, doubtless because the former are often the expression of a congenital constitutional condition which is encountered with such frequency in the various forms of ‘endocrinopathy,’ as also because it may be the consequence of the disease (cancer, syphilis, tuberculosis, etc.) which caused the endocrine lesion or the cachectic condition of the patient when the disease is far advanced.

“6. However, some cases are encountered in which there is excessive secretion of hydrochloric acid in patients with hyperthyroid manifestations and in others with adrenal insufficiency (normal extract of thyroid exerts a stimulating action, and extract of the adrenal capsules an inhibitory action on gastric secretion).

“7. The clinical facts observed by us, and the outcome of the tests carried out by various investigators, permit of establishing a relationship between adrenal insufficiency and gastric ulcer.

“8. In patients affected with adrenal insufficiency we find, as a rule, conditions which are favorable to the development of gastric ulcer. Among these are the lymphatic conditions; changes in the nervous system of vegetative life; the persistence, at times until the hydrochloric acid in the stomach has increased; and, lastly, lowered resistance to infection.

“9. Although we have observed gastric ulcers in

patients with advanced symptoms of adrenal insufficiency, it is not improbable that less important degrees of insufficiency may, in conjunction with other causes (endocrine, infectious, etc.), play an important part in the pathogenesis of certain ulcers of the stomach, as is evidenced by the frequency with which endocrine stigmata are met with in those affected with gastric ulcer.

“10. The pernicious effect exerted by fatigue and the emotions on those patients affected with ulcers and excess of hydrochloric acid may be explained by the adrenal exhaustion which they produce; hence the beneficial effects obtained in these cases by rest and the use of adrenal extracts.”

IV

THE DIAGNOSIS

15.—THE "WHITE ADRENAL LINE"

SOME YEARS ago my friend, Dr. Emile Sergent, of Paris, submitted a manuscript to me for publication in *Endocrinology*, which I translated and published in one of the early issues. I can do no better here than to quote largely from this translation which gives a concise exposition of the importance of this phenomena, the method of its application and its clinical significance.

"It is necessary to follow certain rules which I shall now outline, for only those white lines can be considered as examples of the adrenal line which appear under conditions of technical research similar to those previously indicated, and which present characteristics parallel to those which I have assigned to this particular manifestation.

"To bring about this phenomenon the skin of the abdomen is selected by preference and on it is traced a geometric figure—a rectangle, triangle or cross—thus obviating any possible confusion with lines possibly caused by scars, folds of the skin, etc. Ordinarily I outline a square around the umbilicus with a blunt object, as the rounded end of a fountain pen or, simply the finger tip, taking special care to avoid rubbing, particularly with the nail. The figure should be made by a simple superficial stroking; one must neither bear

down nor scratch. The motion should be deliberate and never rapid. The early or premature appearance of an outline is always a sign of clumsiness, as such treatment strikes and surprises the vasomotors, thus interfering with the reaction instead of causing it. I am in the habit of telling my students that such a procedure is likely to be a source of error.

"When the tracing has been made properly, all movement on the part of the patient is prohibited and one waits a short time. Immediately following the outlining nothing is seen, provided the proper technique has been followed; but after a few seconds, about half a minute, a pale line or band begins to be noticed following the course of the finger (or pen). Gradually this becomes more and more distinct and white, at the same time becoming larger, so that eventually the line exceeds in size the actual area touched by the finger tip.

"This white line attains its maximum clearness in the course of about one minute, and persists for one, two or even three minutes before being gradually obliterated. This, at least, is what is to be expected in well-defined cases of adrenal insufficiency, the only ones, in fact, in which the test has any real value.

"Certain errors may and do result from improper technique. I need only mention those due to an improper degree of pressure exercised at the time of making the tracing; but I wish to direct attention to some causes of error which may be due to various insignificant circumstances.

"Naturally, the lighting plays an important part. In bright daylight or sunlight, or even in bright electric light, it is sometimes difficult to see the white line. It is my custom after having made the tracing, to draw up the sheet or clothing in such a way as to cast a light shadow such as may be produced by a screen. By taking this precaution, I have demonstrated the phe-

nomenon perfectly when a test made just before had failed to disclose it.

"In like manner all factors causing a direct or indirect influence on the capillary circulation of the skin of the abdomen may modify the vasomotor reactivity and, therefore, disturb the conditions favorable to the test. Hence it is useless to seek the line in a subject whose abdomen previous to the test was covered with a poultice, fomentation or compress. A number of minutes should be allowed to elapse after the removal of such applications before making the test. Also in subjects who are clothed one should wait a while so that pressure from the corset or underclothes can have no influence. For that matter, in ambulant cases this local pressure influence is not the only deterrent factor to be looked after, the upright position, fatigue and the effects of walking all have a certain unfavorable influence. In a word, if you desire to follow the exact technique, before making the test place the patient at rest for at least fifteen minutes, with the abdomen free and but lightly covered.

"It seems advisable not merely to outline the rules of technique, but to emphasize the objective characteristics of the 'ligne blanche surrenale,' so that it may not be confounded with other vasomotor conditions from which it must be distinguished. The phenomenon which I originally described must be differentiated from certain white lines accompanied by red lines appearing simultaneously, encircling them or being encircled by them, and preceding or following them. In this connection there will be found in a recent communication by Ravaut and Kronatlinshl read before the Société Médicale des Hôpitaux here in Paris, a detailed study of these various lines.

"The diagnostic significance which I have deduced from my researches is concerned solely with white lines presenting the characteristics repeatedly and

accurately outlined by me—to the white line which I have called 'adrenal.' In attributing to this a pathogenic quality I have considered it purely as a symptom of adrenal insufficiency. To my way of thinking, it is a result of hypotension brought about by the hypoadrenia. To understand the philosophy of its production by such light stroking I have proposed the following explanation: In arterial hypotension we know that there is a peripheral vaso-dilatation; if we begin to produce a light stimulation of the skin, vaso-constriction will replace the vaso-dilatation. . . .

"In pathology as well as in clinical medicine there are no pathognomonic symptoms, in the absolute sense of the term. Diseases are recognized by the presence of a group of symptoms, and these symptoms of the same disease do not necessarily show themselves in exactly the same manner in every case, for here a certain symptom may be absent, and there another. However, some symptoms are more constant and consequently of greater value than others, and this is the case with the white line in the syndrome of adrenal insufficiency.

"Is it then, sufficient ground upon which to base a diagnosis? To answer this definitely would be exceeding the scope of this paper, and going a little too far. As I have said before, and as I maintain, when I determine the presence of the 'ligne blanche surrenale,' my attention is quickened and immediately I begin to look for the other signs of hypoadrenia, such as melanoderma of the Addisonian type which, in turn, causes me to look for other evidences of Addison's disease. This does not necessarily prove that the melanoderma cannot be present save in a typical Addison.

"Again, rose spots have a symptomatic value conceded by all clinicians in the diagnosis of typhoid fever. Does this mean that typhoid cannot exist without being accompanied by these rose spots, or that these

same spots can not be found in other diseases than typhoid? Are all tachycardias necessarily of thyroid origin? Nevertheless does not the discovery of tachycardia stimulate us to look for other symptoms of the Basedow syndrome?

"I wish here to warn the profession against a somewhat growing tendency to seek the absolute in clinical medicine. The clinic only permits an approximation; possessing neither an absolute sign of value, nor an incontestable diagnostic measure; but it strives rather to group signs and syndromes and to associate with them the results of functional action and reaction.

"It is only with such ideas in mind that we should seek to demonstrate the 'ligne blanche surrénale,' and that we will be able best to appreciate its diagnostic value."

In commenting on this white line of Sergent, Dr. P. Harvier, in his treatise "Sympathique et Glandes Endocrines," remarks that the white line does not exist in all cases of hypotension. According to Castaigne, it indicates vascular collapse, the diminution of the angiotonic function, whereas hypotension expresses an insufficiency in the cardiogenic function; but when this white line is noted in conjunction with hypotension and a more or less marked degree of asthenia, it presents a considerable diagnostic value.

While Sergent's method was first announced several years ago, it does not seem to have attained much popularity in this country, though it is often referred to in French journals. Despite this, the measure may be of much value especially, for instance, in studying serious symptoms-complex following the acute infectious diseases. The test as here described has the advantage of extreme simplicity and convenience, plus a diagnostic value which is most serviceable.

This measure is not infallible. It merely supplements other clinical findings or stimulates our diagnos-

tic search, as the case may be. It is a simple and altogether worth-while procedure, worthy of routine application in the study of all asthenic states and, in fact, in a majority of the chronic disorders.

16.—OTHER SKIN MANIFESTATIONS

Besides Sergent's "white adrenal line," mentioned in the previous chapter, there are certain other skin manifestations in adrenal diseases. Urticaria and other severe vasomotor skin symptoms are among the well-marked findings in persistent hyposphyxia, while lesser degrees may cause flushings and sensations of passing distress localized in various areas of the skin. The adrenal origin of some forms of urticaria is seemingly confirmed by the occasional "miraculous" disappearance of large and most uncomfortable wheals following a single hypodermic injection of from five to ten minims of adrenalin solution.

In well advanced cases of progressive hypoadrenia, which is really another name for the disease we have been taught was first named by Addison in 1855, which, like all organic diseases, may be seen in differing forms and stages, there is a localized bronzing of the skin and mucous membranes due to the deposition of a dark pigment of undecided origin. Happily, this disease is rare, as unfortunately its outcome is hopeless, though temporary relief has followed adrenal medication.

Sergent says of this condition: "On the one hand, Addison's disease is inseparable from melanoderma; without melanoderma, no bronzed disease. The bronzed disease is not irrevocably linked up with the existence of destructive lesions of the adrenals; lastly, melanoderma has never been able to be produced by the experimental destruction of these glands."

Since melanoderma, extreme asthenia, and the "white line of Sergent" constitute the syndrome,

nearly always more or less chronic in its nature, which is everywhere recognized as Addison's disease, it may be well to remember that Addison's disease may not always present a chronic manifestation and that it may exist without the melanoderma. Notwithstanding the above quotation from Sergent, he reported a case diagnosed as Addison's disease which did not produce a bronzing of the skin.

"The patient was a man, aged 20, suffering from a pultaceous tonsillitis without complications, from which he rapidly recovered. The very day he was to leave the hospital, seemingly entirely recovered, he presented symptoms of exceptional gravity which were such as to lead one to suspect poisoning: vomiting, diarrhea, cyanosis and chilliness, dyspnoea, syncope. On the following day he died suddenly while sitting on his bed. At the postmortem no trace of poisoning was found; the one and only lesion visible was located in the adrenal glands, which were entirely destroyed by tuberculosis and transformed into caseous masses."

Though the melanoderma was lacking in this patient, the author felt compelled to diagnose it as Addison's disease. He says, further, "We were able to find among the various writings several similar observations."

We are publishing here Dr. Jacques Carles' report of two cases of Addison's disease, which most decidedly exhibited this discoloration of the skin. These are of added interest in this connection, because they both, at least partially, recovered. Note the violent nervous, gastric and psychic results of poisoning, as profound asthenia, cyanosis and chilliness, vomiting, and sometimes melanoderma with or without pigmented buccal patches; for without this discoloration the observer might easily mistake the diagnosis, thinking it to be the result of poisoning.

The one case is as follows: The subject bore a very

intense melanoderma; intrabuccal pigmented patches; marked asthenia; considerable hypotension; vomiting and lumbar pains with emaciation; incapable of intellectual effort; and it looked as if he would rapidly succumb. After three months' treatment his functional condition improved to such an extent that he was able with ease, and uninterruptedly, to perform the duties of a responsible clerical post in the service.

The other case reported was one of Dr. Carles' patients in the Hospital Saint Marthe. He had been apparently cured about a year previously, and seemed to be able to resume active service in the trenches, but at the end of a few weeks he experienced a serious relapse. This time the treatment was practically without effect. Notwithstanding the fact that the patient was set to work for a prolonged time, he gradually became as black as a negro; his mucous membranes were heavily pigmented; he remained asthenic, emaciated, and numerous forms of cervical adenopathy appeared.

17.—CIRCULATORY MANIFESTATIONS— HYPOSPHYXIA

The important part that the adrenals play in the circulatory apparatus has been too generally recognized to demand a reiteration here. The "kinetic system"—the name that Crile gave the system in the body that is evolved primarily for the transformation of latent energy into heat—includes the adrenals.

The control of the circulatory apparatus lies largely with the endocrine glands. The sympathetic system, and the numerous neurocirculatory phenomena that it controls, is really dependent upon endocrine and particularly adrenal function.

Among other things, it is the function of these glands to regulate the tonicity of unstriped muscle, including that of the heart, blood-vessel walls, and alimentary

canal. In fact, all muscles, voluntary or involuntary, are affected by the adrenal principle.

These glands are influenced very decidedly by toxic substances which may get into the circulation. As a matter of fact, it is the function of the adrenals to respond immediately to toxic stimuli in order that the body's defensive and detoxicating mechanism may be started in its necessary work as soon as possible. As the result of this, the administration or release of various poisons causes an increase in the work of the adrenal glands with circulatory changes which are very well known as well as other changes in oxidation which are made necessary by the toxemia.

The circulatory manifestations in asthenic cases—those suffering from hypoadrenia—are easily recognizable. The patients are tired out and unable to accomplish their usual mental or physical work. They have an aggravated degree of muscular fatigue which extends to the involuntary muscles, causing heart weakness (very commonly these cases are classed as "myocarditis" when in reality there is no real structural change in the heart muscle at the time), the vessel walls lose their tonicity and as a result there is a condition of low blood-pressure which in turn causes cold hands and feet and other evidences of circulatory insufficiency.

Adrenal substance is administered to persons having hypoadrenia because it exerts a musculo-tonic effect. It slows, steadies and strengthens the heart; it raises the blood-pressure, and, by actual measurement, increases the elimination of wastes.

Hyposphyxia is essentially the circulatory picture in adrenal insufficiency. The term was developed and first brought into prominence by Prof. A. Martinet, of Paris, late in 1912.

Briefly, hyposphyxia is a modified form of asphyxia, hence its name. The stimuli which regulate circulation,

cardiac efficiency and the blood-pressure are deficient, the circulatory mechanism "lacks punch." This, it is believed, is largely due to a form of pluriglandular insufficiency in which the adrenal element is prominent. Hyposphyxia, then, is closely allied to hypoadrenia.

From the standpoint of symptomatology it seems that the above position is perfectly reasonable. The principal clinical manifestation is a decided degree of circulatory insufficiency. While the symptoms may not be identical in all cases, they are certainly quite similar: Poor circulation with bluish-colored and cold extremities, cardiac asthenia and hypotension, subnormal temperature and evidence of stasis due to poor circulation. With this invariably goes asthenia (due to poor cellular nourishment because of the bad circulation and, more important still, deficient hormone production with consequent reduced sympathetic function and generally slowed metabolism) and the usual findings of hypocrinism.

As a disease-picture per se, hyposphyxia is not common, for the good reason that other conditions so commonly accompany it that they are the ones that are seen and treated. I do not quite agree with Martinet that hyposphyxia is deserving of classification as a disease; but as an extremely important syndrome which complicates so many chronic disorders it is assuredly important and worthy of the same kind of intensive study and clinical appreciation that our French confreres have given it.

The treatment consists in reducing the insidious causative conditions which through toxemia or some other cause depleted the output of the hormones which regulate the circulatory department; the mechanical removal of stasis by means of massage, exercise, etc., the stimulation by means of homostimulative organotherapy of the glands which are largely at fault (whether as a cause or an effect) and good hygiene.

V

TREATMENT

IT IS obviously not within the province of this monograph to prescribe the general treatment for the diseases discussed herein. My readers are not in need of instruction from me in this regard, but I merely wish to make a few suggestions as to the organotherapy that is being used successfully in the treatment of these conditions.

Asthenia. In the treatment of this disease many physicians are inclined to reassure their patients and satisfy their own consciences by saying, "What you want is a good rest. Lay off your work for a while and take it easy. You'll be all right." This may be good practice, for obviously rest is the antithesis of fatigue; but to my mind it is not enough. As has been said, there is an important endocrine factor, the recognition of which "permits organotherapeutic treatment," and which, as stated by Laignel-Lavastine, "permits the cure of a large number . . . ticketed neurasthenics, etc." Rest is negative treatment. It merely allows Nature to have a better chance. Organotherapy, on the other hand, is positive treatment, since it definitely encourages those endocrine organs which have been overworked, and actively favors the restoration of the deranged balance.

Rest is good; but rest plus organotherapy is better; and quite the best of all is to add to these two essential

measures, the removal as far as possible of every source of toxemia whether from a focal infection, from ingested poisons or from the alimentary canal.

The French are in the habit of giving combinations of synergistic glands for the especial purpose of encouraging the all-essential functions of the endocrine glands which they are convinced are below par in all "run-down conditions."

Hyposphyxia. The treatment of this condition has been briefly referred to in Chapter 17, i. e., the mechanical removal of stasis by means of massage, exercise, etc., the stimulation by means of homostimulative organotherapy of the glands which are principally to blame for the condition, either as a cause or an effect, and, of course, good hygiene.

A great many clinicians now are getting good results from the administration of a pluriglandular compound containing the adrenal principle—for hypoadrenia is the rule in these syndromes; a small dose of thyroid, which is complementary to the adrenin and stimulates oxidation; and spermin, the active principle of the interstitial cells of Leydig which is well called "a cellular punch-producer." This pluriglandular formula increases circulatory efficiency, raises tension and is an "anti-asthenic remedy."

Postinfluenzal Asthenia. The fact has been mentioned that a good habit to form in the treatment of this condition is to take the blood-pressure, and when low blood-pressure and asthenia are found together, with the development of a subnormal temperature and considerable reduction in the alimentary wastes (urea and total solids), besides hygienic, dietetic and medicinal treatment add the measure which I have called "adrenal support." The pluriglandular tonic that has been used so successfully in hyposphyxia and asthenia, has also proved very efficacious in postinfluenzal asthenia.

Pneumonia. The pulse arterial tension should be watched very carefully as an index of the condition of the adrenal glands, and while it is not an easy matter to prevent adrenal depletion, no harm can be done by taking the adrenals into consideration.

Sajous, in the *New York Medical Journal*, said that upon pneumonia and other infections which involve the respiratory apparatus particularly, the adrenal and the thyroid glands have a very great bearing. In pneumonia, death is due primarily to adrenal failure, as expressed by "rapid lowering of the arterial tension, marked lividity, edema of the lungs and extreme asthenia." Dr. Sajous' views on this subject certainly harmonize with the mortality records in which the senile form of the disease predominates. It is well known that the senile are prone to succumb for the reason that in old age the adrenals are functionally deficient. And support with the corresponding extract is warranted on this assumption.

War Adrenal Insufficiency. The treatment of this condition has been given rather detailed consideration in Chapter 11, but we will briefly summarize. Carles made the statement that low blood-pressure is common among all the men at the front, but the terrific strain put upon them sent the blood-pressure of those whose systems were none too strong, down to the danger point. Weeks of complete rest and quiet were necessary in treating these cases, and it was some months before the men were capable of reading a paper, writing a letter or even answering questions that required thought. Carles also withheld meat from the diet of the cases he was treating. An astonishingly rapid improvement was noticed under adrenal therapy. It was observed, however, that the resumption of active service was likely to rearouse the old trouble, and that the second attack might prove grave beyond recuperation.

Malaria. Nicola Pende, Italy's leading endocrinologist and the author of the most comprehensive treatise on this subject, urges the routine consideration of the adrenal functions in malaria. In fact, he begins his treatment by supporting adrenal function. He insists that a large share of the success of his method fully outlined in the article, is due to the early adrenal medication which "wards off the vasomotor collapse" not merely from the quinin used but from the severe toxemia of the disease itself. For it must be remembered that quinin is a poison just as are the protozoal toxins.

Many authors claim good results from the administration of spleen therapy in the treatment of malaria. One author has gone so far as to say that it produces the good effects of quinin without its bad effects. Nouveau claims that it is superior to quinin, arsenic or iron. Paucot, of the French Army Medical Corps, has used spleen therapy and writes on the subject as follows:

"This treatment has given me results incomparably superior to those which I have secured from other methods of treatment. It seems to succeed in every case of chronic splenitis, save only where the spleen has acquired a stone-like hardness and has become adherent to the diaphragm or abdominal wall. Even then, however, there has been amelioration. The general condition is rapidly benefited. The men are so thoroughly cured that they are able to continue their service, thus obviating a considerable expense and loss of men to the government."

Lambelle, of the British Royal Army Medical Corps, reports good results following the use of the pancreatic ferments, trypsin and amylopsin hypodermically. He says, "Clinically, the results are most marked. The change in the patient within a few hours is remarkable and the benefit permanent.

A pluriglandular formula containing thyroid, be-

cause of the well-known antitoxic and protective functions of this gland, adrenal substance and spermin is being used with considerable success in this serious infection.

Diabetes. The dietary treatment of diabetes is too well known to discuss here.

Kingsley, in discussing the therapeutic possibilities of secretin, called attention to the fact that many attempts had been made to use secretin in diabetes because its characteristic action on the pancreas was supposed to extend beyond its well-known enzyme-stimulating effects and to increase the internal secretory powers of this gland. It has been used in a number of cases of diabetes, but almost universally had no effect upon the sugar in the urine. On the other hand, diabetics using it gained in weight from ten to twenty pounds and were greatly improved in general health. It was hard to reconcile these two observations, and an explanation of the good results is found in Beveridge's paper, which was under discussion, which tells of the favorable action of secretin on protein metabolism and in relieving intestinal stasis and the accompanying toxemia.

A large number of tests have been made with different pancreatic products—from the total gland, from the head, from the middle, and from the tail—and the results indicate that the impression gained from the histologists' statements is correct, and that an extract of the tail of the pancreas is, indeed, a more efficient therapeutic remedy in diabetes than that made from the total gland. It is for this reason that I use an extract of the posterior third of the pancreas, prepared especially for its glycolytic influence, rather than for any enzyme value that it may have.

Starling and his colaborers have unquestionably demonstrated the fact that the duodenal hormone exerts a decisive physiological influence upon the pan-

creas as a whole. For many years it was believed that the activation of the pancreas enzymes was the main field of activity for the hormone, secretin. Within the last few years a number of papers have been published, indicating that the administration of secretin exerts a still more subtle and broader influence upon the metabolism of sugar through some effect that it exerts upon the internal secretory powers of the pancreas. With this in mind, the therapeutic possibilities of the administration of pancreas tail substance seem to be properly supplemented by the administration of secretin. A pluriglandular formula of this kind has been used for a number of years by several interested clinicians, and by varying the amounts and origin of the various pancreatic ingredients, we have hit upon a formula which we believe is of optimum value.

In addition, we have added a small dose of tonsillar substance, which has been tried out by some empirical physicians and recommended by several German authorities as indirectly bearing upon glycolysis. This is retained in the finished product—Pan-Secretin Co. (Harrower).

There is one other matter which deserves consideration in the treatment of every diabetic case. I refer particularly to the extreme necessity of remineralization. It will be recalled that acidosis is frequently the cause of death in diabetes and that every individual with diabetes mellitus has a tendency toward a deficiency of the alkaline reserve and consequently to an excess of acid substances of the disturbed metabolism. A preparation containing magnesium phosphate, calcium phosphate and glycerophosphate, potassium bicarbonate and sodium bicarbonate has proved to be a worth-while preventive as well as a remedial measure in diabetes.

VI

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