1937

Problems of adrenal cortical insufficiency / John W Henderson

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THE PROBLEMS OF ADRENAL CORTICAL INSUFFICIENCY

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SENIOR THESIS

1937

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INTRODUCTION

The recognition of the symptoms of suprarenal cortical insufficiency is not recent. The syndrome of insufficiency which is associated with tuberculous lesions of the suprarenal bodies was first described by Addison (1855). It was not recognized at this time, however, that the suprarenal bodies were composed of two distinct physiological entities. Accordingly the investigative work at this time was confusing and misleading. When, however, the double makeup of these structures was recognized, the medullary portion received the most attention. As it became obvious that the adrenal medulla was not an essential factor in the maintenance of life, the syndrome which is now recognized to be associated with partial absence or destruction of the adrenal cortices took on new importance. The evolution of these ideas, however, occupied a space of approximately seventy years. Thus the rational therapeutic approach to suprarenal cortical insufficiency as a distinct entity separate from the adrenal medulla and its secretion, epinephrine, becomes a development of the last decade. So deeply rooted, however, was the opinion as to the essential relationship between the medulla and the syndrome of cortical insufficiency, that clinicians continued to employ epinephrine in the treatment of this disease as late as 1932. The problem of adrenal insufficiency from the standpoint of cortical function and therapy, therefore becomes very recent.

The very nature of the evolution of this problem favored numerous investigations of varying worth. The therapeutic aproach to the problem, alone, has undergone a profound change since the first early reports. To keep astride the ever changing viewpoints and the voluminous literature on this subject, has been difficult for the average physician. As an assimilation of the literature and a review of the problem to date, this paper is presented.

HISTORY

The first approach to the therapy of suprarenal cortical insufficiency was made before the beginning of the present century. Investigation was mainly confined to the British Isles. Jones (1895) reported a case of Addison's disease which was treated with dessicated whole suprarenal gland substance. He reported the patient to be vastly improved within a month following this regime. Stockton (1895) had a patient who ingested two to three raw sheep adrenals daily in sandwiches. The author believed definite improvement was evidenced. Oliver (1895) reported a case which was given an alcoholic extract of suprarenal glands. Bramwell (1897) injected 15 minims of sterilized suprarenal capsule juice into a patient twice a week. Later on, this preparation was administered every other day by mouth. The patient apparently showed marked improvement on this weak alcoholic extract but died from influenza. Autopsy showed complete absence of the suprarenal capsules. It is quite probable that these early attempts at treatment were of some benefit, since many of the more modern extracts employ the use of alcohol as an extraction medium.

GENERAL CONSIDERATIONS

Although primarily concerned with the therapeutic aspects of adrenal cortical insufficiency, some knowledge of the symptomatology and pathological physiology is essential to enable the reader to properly evaluate the factors involved in therapy. It is by correlation of the symptomatology and pathology that much of the investigative work directed along the lines of therapy has been evolved.

Symptomatology

The symptomatology of adrenal cortical insufficiency, as here presented, includes a combination of both clinical and experimental observations, Snell (1934), Hartman (1933), Rogoff (1934), and Wiggers (1934). It is essential that the reader keep in mind that in the human subject, the loss of suprarenal cortical function is partial and chronic, as contrasted to the acute and absolute insufficiency in experimentally adrenalectomized animals.

The majority of investigators agree that the foremost symptoms of cortical insufficiency are asthenias of the nervous, muscular, and circulatory systems, accompanied by gastro-intestinal disturbances. The first evidence of the disease is usually some degree of anorexia. This loss of appetite may be so severe that there occurs a complete aversion to fatty foods. Diarrhea and vomiting may accompany these symptoms. Loss of

weight and emaciation soon appear and are associated with ready fatigue upon exertion. The muscular asthenia may be so profound that unnecessary voluntary movements of the sufferer become completely absent. Examination of the circulation reveals a weak heart action and a systolic blood pressure in the neighborhood of 70 to 80 mm. of Hg. With progressive increase in the muscular asthenia and gastro-intestinal symptoms, nervous phenomena finally develop. The latter include varying degrees of muscular twitchings, hallucinations, lethargy, and coma. A peculiar pigmentation, ranging in color from bright yellow to a bronze-brown, is seen in some cases especially prevalent on the exposed portions of the body.

In the human cases, the course of the disease is marked by remissions and relapses. Indeed, the remissions may be so complete as to suggest a recovery from the adrenal cortical insufficiency.

Pathological Physiology

The concept of the pathology underlying the above described symptoms is, today, still incomplete. It is generally agreed that the lack of suprarenal cortical hormone is an important factor, but the precise effect of such an absence of hormone has not been definitely established. The investigations which have been carried out with the object of ascertaining the pathology which occurs with insufficient cortical hormone have been prac-

tically all experimental in nature. Many of the earlier views are today untenable. Nevertheless, a complete resume of the work done to date will be presented, that the reader may more easily comprehend the evolution of ideas.

For purpose of convenience, the many theories that have been advanced as to the true nature of suprarenal cortical insufficiency can be roughly segregated into five groups. These groups associate cortical insufficiency with failure to maintain the circulatory and water balance in the animal, alterations in carbohydrate metabolism, upset in mineral balance, derangement of kidney function, and disturbance of urea and nitrogen ratios.

Chief among the earlier theories as to the underlying pathology of cortical insufficiency, is that associated with disturbance in the fluid and circulatory balance of the body. This theory gained prominence through the work of Corey (1927) and Marine and Baumann (1927). Corey postulated that since forcing fluids prolonged the life of his adrenalectomized animals, that the underlying mechanism of the symptoms was due to a dehydration, thus allowing for the accumulation of toxic substances in the animal. Marine and Baumann likewise concluded that diuresis was one of the important factors determining the survival of their experimental animals. They likewise concluded that the initial loss of fluid from the body after experimental adrenalectomy was associated with acidosis. Britton (1930) in a general review of

the problem also recognized that there was a tendency towards increased concentration of the blood and acid intoxication. This explanation, however, was not generally accepted by the majority of investigators as the fundamental alteration with the exception of Swingle. Swingle et al: (1933) (1934) strongly championed the theory that the suprarenal cortical hormone was primarily concerned in the regulation and maintainance of a normal circulating volume of fluid. As a manifestation of this change, they cite the decrease of blood pressure which is so often observed. In their conception the diminished circulation volume was due to the inability of the adrenalectomized animal to draw fluid back into the blood stream from the tissue spaces. This explanation was so applicable in their opinion that they say, "It is our opinion that all the manifestations, symptoms and physiological peculiarities, which occur in adrenal insufficiency (experimental), are merely results of a progressively failing circulation due to decreasing volume of circulating fluid." Swingle et al: (1936) working with dogs, found that cortical hormone administration in large quantities affected a redistribution of fluids in the body of the suprarenalectomized animal.

The possibility that the kidney was intimately connected with the symptoms attendent upon the removal of the suprarenal cortices, has likewise been long considered. The theory of kidney dysfunction has been closely associated with the alterations in the circulatory

balance previously stated. Swingle (1927) first postulated the failure of kidney function as the cause of the acidosis which appeared in his adrenalectomized animals. Harrop and his co-workers in conjunction with Swingle and Pfiffner (1931) believed that the results of experimental cortical insufficiency indicated either a direct or indirect influence of the adrenal cortex on kidney function, especially in the excretions of fluids, chlorides, and urea nitrogen. Swingle and Pfiffner (1932) observed that renal insufficiency was a constant finding after adrenal ablation. These investigators were unable to demonstrate any significant anatomical lesions in those animals dying from adrenal insufficiency, and assumed that the renal lesion, if such was present, was a functional one. In the following year, Swingle et al: (1933) presented their theory of the alteration in the circulatory and fluid balance of the body as the underlying factor in cortical insufficiency and considered the renal disturbance as a secondary manifestation. Harrop et al; (1933) took a more conservative viewpoint and considered the kidney as the locus of the regulatory mechanism exerted by the adrenal cortical hormone. The kidney in turn was considered to participate in the regulation of the electrolyte balance and fluid distribution of the body.

It has been rather well established that there is a rise in the non protein nitrogen and urea nitrogen in the adrenalectomized animals by the work of Britton (1930), Harrop et al; (1932),

Swingle and co-workers (1933), and Koelsche (1934). None of these workers considered the alteration in the nitrogen levels as the fundamental change which occurred in experimental cortical insufficiency, but rather as a secondary manifestation. Harrop et al; (1932) however, used the nitrogen concentration of the blood as a method for determining the efficacy of their treatments in suprarenalectomized dogs. They considered a decrease of the urea nitrogen and non protein nitrogen to normal as the earliest indication of the recovery of their animals from cortical insufficiency. Koelsche (1934) believed the cortical hormone to exert a sparing action on nitrogen metabolism.

The theory that absence of suprarenal cortical hormone was concerned with a disturbance in carbohydrate metabolism was first suggested by Britton (1930) when he observed the diminution of liver glycogen and blood sugar in adrenalectomized animals. Although it was generally accepted by the majority of investigators, that such a diminution of reserve sugar occurred in those animals suffering from cortical insufficiency, no one regarded such an alteration as being the fundamental pathology with the exception of Britton. Britton and Silvette (1931)-(1932) found that the blood glucose and liver and muscle glycogen were considerably elevated within an hour after extract treatment of their adrenalectomized rats. The storage of liver glycogen, alone, "was enhanced three to five times above that found in the

controls." They believed the disturbance of carbohydrate metabolism was primarily responsible for the death of the untreated animals. They came to the conclusion that the life preserving function of the cortical hormone was primarily concerned with the maintenance of a normal carbohydrate balance in the body. Theseconclusions were not generally accepted by other investigators. Britton and Silvette (1934) made their most vigorous defense of the theory. They believed the general decompensation of the organism which follows adrenalectomy to be on the basis of carbohydrate deficiencies of a fundamental nature. They did not consider tenable the possibility that the carbohydrate disturbance was secondary to the general disorganization of the organism following suprarenalectomy, as was held by other investigators. These workers were strong opponents of the circulatory theory of Swingle et al; (1933)(1934) since the administration of large amounts of saline injections into their animals restored the circulatory volume but did not effect the survival period. The great drawback to Britton's and Silvette's proposals, however, was that they admitted, "Glucose solutions are apparently ineffective in the treatment of adrenalectomized animals." Zwemer (1934) considered the changes emphasized by Britton and Silvette (1934) to be terminal phenomena rather than fundamental in character, and expressed the opinion that alterations of carbohydrate mobilization should be considered as just

one of the many functions of the adrenal cortex hormone in the maintenance of life. Harrop (1935) believed that the cortical hormone had no direct influence on carbohydrate metabolism.

Of all the theories as to the possible underlying mechanism of adrenal cortex insufficiency, that concerning the disturbance of mineral metabolism has received the most comment. Most all of the investigators working in the field of experimental adrenalectomy have, at one time or other, been involved in its discussion. This hypothesis was first suggested by Marine and Baumann (1927) who considered that sodium salts might have a specific action in prolonging the life of adrenalectomized animals because of their success in the employment of saline solutions as a therapeutic agent. Britton (1930) recognized the tendency towards increase of serum calcium and the reduction of blood chlorides in animals suffering from adrenal insufficiency. Harrop and his co-workers (1931) also suggested a direct or indirect influence of the adrenal cortex in the excretion of chlorides. It was not until the work of Loeb et al; (1933) however, that the problem received extensive consideration. These investigators considered the loss of sodium from the body by way of the urinary secretion to be an important factor in the development of the clinical picture of adrenal insufficiency in the dog. They considered the mechanism of the loss of sodium to be on the basis of three possibilities, (1) "fixed base is called upon to

participate in the excretion of large amounts of acid", (2) "loss of sodium is secondary to the loss of water through the kidneys", (3) "that the loss of sodium is primary i.e. that the adrenal glands exert a regulatory effect upon sodium metabolism analogous to that of the parathyroid glands upon calcium and phosphorus metabolism". They believed the first theory to be untenable because investigative work showed no significant accumulation of abnormal acid radicals in the blood. The second theory was believed unlikely since their investigations showed the loss of sodium from the body to be notably greater than the loss of water, and furthermore, with primary dehydration an increase rather than the established decrease in the concentration of sodium in the blood under these circumstances would be expected. They concluded that the third hypothesis offered the most satisfactory explanation for the behavior of the base sodium in adrenal insuffieiency. Loeb et al; were also of the opinion that the loss of chloride ion parallelled the loss of sodium ion but not in equivalent amounts. Their work also indicated an increase in the potassium ion in the blood. Hartman (1933) commenting on the problem, recognized a change of the sodium and potassium ions but did not consider this change to be specific either as a test for adrenal insufficiency or as a primary cause of the condition. Harrop and his co-workers (1933) keeping their suprarenalectomized dogs on a carefully measured food intake, found an increased

excretion of sodium chloride following cessation of cortical extract. They found that the electrolyte balance could be restored by the readministration of cortical extracts. These workers believed that the loss of salt in suprarenal insufficiency was analogous to the collapse due to exposure to high temperatures in which great loss of salt occurs through the sweat. They were of the opinion that at least one of the functions of cortical extract in the suprarenalectomized dog was a participation in the regulation of the sodium and chloride metabolism and consequently of the balance and distribution of water. Harrop et al; came to theconclusion that loss of electrolytes could not be taken to be the cause of death in suprarenal insufficiency but the evidence to date indicated it to be an important factor in the general syndrome. Rubin and Krick (1933) in an analysis of the blood of rats suffering from experimental insufficiency, found a loss of calcium, magnesium, sodium, potassium, phosphorous, chloride, and nitrogen. Although they considered it a possibility, they did not believe the primary action of the cortical hormone to be one of salt regulation. Zwemer and Sullivan (1934) believed the syndrome of adrenal insufficiency, chemically, to be a disturbance of salt and water metabolism, with loss of water and depletion of sodium and blood chloride, together with an increase of potassium. This latter finding, in regard to potassium, is in agreement with the findings of Loeb et al; (1933) and in disagreement

with the opinions of Rubin and Krick (1933). Zwemer (1934) reaffirmed his opinion that the adrenal cortex had a regulative effect on the salt and water metabolism of the cell. Harrop et al; (1935) after extensive experimentation with the suprarenalectomized dog, found that a normal concentration of both plasma sodium and chloride were required for the maintenance of the animals. They state, "If the chloride falls anorexia appears and hypoglycemia eventually results." "Fall in plasma sodium is accompanied by dehydration and hemoconcentration." They postulated that the loss of chloride from the blood had an intimate bearing on the secretion of hydrochloric acid in the stomach of the dog, thus explaining the anorexia. These workers were one of the first to link their experimental findings with the clinical symptomatology. Harrop et al; (1935) came to the conclusion that suprarenal cortical hormone was probably concerned with the regulation of sodium excretion by the kidney, and thus eventually with the proper maintenance of water balance in the organism. Kendall and co-workers (1935) because of their success with a crystalline compound in the treatment of insufficiency, believed a disturbance of sodium chloride metabolism to be intimately associated with the condition. Wilder et al; (1936) using clinical materials for the basis of their assumptions, found that administration of a diet high in potassium content, produced a sharp decrease in serum sodium and plasma chloride and a rise in serum

potassium, accompanied by the appearance of acute suprarenal insufficiency. Swingle et al; (1936) however, disagreed with this theory because they observed no change in the sodium and chloride levels of the plasma in ~~his~~ their animals treated with cortical hormone and on a salt free diet. The investigations on the electrolyte theory are brought up to date by the work of Harrop et al; (1936) who found a urinary loss of sodium and chloride, and a retention of potassium and nitrogen in their untreated suprarenalectomized dogs. Their work suggests that more emphasis should be placed on the potassium balance. They state, "The reinjection of cortical hormone in suprarenal insufficiency causes an active renal excretion of potassium which is greatly in excess of the probable extra accumulation of this component in the extra cellular fluids during the period when insufficiency is developing.

It is thus evident that the underlying pathology of suprarenal cortical insufficiency is still incomplete. Certainly little correlation exists between the theories of insufficiency and the clinical symptomatology. It must be admitted, however, that rapid strides are occuring in this problem and that the considerations, to-day, are much more advanced than six years ago. In summarizing, the present investigations indicate a rather fundamental relationship between the suprarenal cortical hormone and and the sodium, chloride, and potassium balance of the blood.

The regulation of carbohydrate metabolism, fluid balance, and urea and nitrogen levels appear to be only a secondary relationship. That the kidney plays a part in this syndrome is also indicated.

ADRENAL CORTEX EXTRACTS

As a necessary measure in the study of suprarenal cortical insufficiency, the various suprarenal preparations should be discussed. Much bitterness has been aroused between the investigators in this field over the usefulness of their respective preparations. It is to be regretted that more cannot be said about the usefulness of the commercial preparations which are available today. For convenience of study, the preparation, assay, administration, and relative potency of the various extracts will be taken up in their respective order.

Preparation

Much dispute exists as to the investigator who first prepared an extract of the suprarenal capsule which demonstrated therapeutic properties in adrenalectomized animals. As nearly as the writer can determine, the honor belongs jointly to Rogoff and Stewart, and Hartmann, MacArthur, and Hartman, who published their results in 1927. The former group of investigators extracted dog adrenals with physiological salt solution and glycerine. They proposed the name "interrenalin" for this product. Hartman and co-workers made sodium chloride extracts of ox adrenals which supposedly contained no epinephrine. They believed the essential hormone of the adrenal cortex to be present in their preparation and proposed the name "cortin" for this hormone. The results of these investigations created a

desire on the part of many workers to be the first to prepare an extract suitable for commercial manufacture. In this activity Rogoff and Stewart took no part, but were satisfied to perfect their new preparation and to confine its use to experimental work. Hartman and co-workers, and Swingle et al; were chief among those who attempted commercialization. Swingle and Pfiffner (1930) first prepared an aqueous extract of beef adrenals. Hartman (1930) likewise prepared an aqueous extract, because of the sodium chloride content of the old preparation necessarily limited the degree of concentration. Britton (1930) in a review of the work done up to that time, evaluated the results in the following manner, (1) "approximately 150 to 300 times the amount of cortex normally present in the animal has been administered", (2) "the extract to date has been shown to be effective only when adrenalin is contained in it", (3) "it has not yet been fully ascertained that indefinitely long survivals are possible with the use of these extracts." Swingle and Pfiffner (1931) advanced a step forward when they introduced permutit filtration as a means for removing the epinephrine during preparation. Britton and Silvette (1931) examining both the preparations of Hartman and Swingle, found the product of the latter investigator to be more easily prepared. Britton (1932), however, was of the opinion that the Swingle-Pfiffner method of extraction was slow and believed that the

resulting preparation was much too expensive, the cost of 100cc being about thirty dollars. Grollman and Firor (1933) introduced a method of extraction which they believed to be much simpler and more efficient. They used acetone as an extraction medium because of the relatively small amount of extraneous fatty substance which remained after its use. They also introduced the use of alkali instead of permutit filtration as a method for the removal of epinephrine. Pfiffner et al; (1934) also employed acetone as an extraction medium. Grollman and coworkers (1935) introduced a simple method for absorbing the adrenal cortical hormone on charcoal, thus making it suitable for oral administration. In the work of Pfiffner et al; (1935) is described a method of extraction which will serve as an example of the more modern methods of preparation. "Whole beef glands are extracted with alcohol. The aqueous sludge resulting from the removal of this solvent is extracted with benzene, which leaves most of the adrenalin behind. The residue from the benzine solution is extracted with acetone. The acetone-soluble material is distributed between petroleum ether and 70 percent alcohol. The alcoholic phase which contains the hormone is freed from adrenalin and certain impurities with permutit. Further purification is effected by distribution procedure, taking advantage of the solubility of the hormone in both aqueous media and solvents such as ether and benzene."

Assay

The biological assay of adrenal cortical extracts have been chiefly confined to such animals as the dog, cat, and rat. Grollman and Firor (1933) utilized the rat method of assay, the average amount of extract necessary for normal growth in a 50 gram adrenalectomized rat was defined as a rat unit. This method of assay has not been generally accepted because of the frequent occurrence of accessory interrenal tissue in this animal. Harrop, Pfiffner, Weinstein, and Swingle (1932) proposed a method of assay based on the earliest indication of a rise in blood non-protein nitrogen and urea nitrogen in the adrenalectomized dog. Their method of assay has been the most widely accepted. They define a dog unit as "the minimum daily kilogram dose of cortical hormone necessary to maintain normal physiological conditions in the bi-adrenalectomized dog for a period of seven to ten days; the two criteria of normal physiological conditions being maintenance of body weight and blood level of non protein nitrogen (or urea)."

Administration

The early cortex extracts were crudely prepared and not suited for human usage. Almost four years elapsed from the time of the first preparation until Swingle and Pfiffner (1931) reported an aqueous extract suitable for subcutaneous or intravenous administration in man. With this work as an impetus, investigation

proceeded rapidly in the refinement of cortical extracts. Rogoff (1932) first reported the use of cortical extract by oral administration. Using the extract of his own manufacture, he was impressed by the fact that oral administration of the extract proved more valuable, in compensating for lack of cortical hormone, than parenteral administration which was used by all other investigators. Britton (1932) discussing Swingle's and Pfiffner's extract, admitted that the preparation was effective when given by mouth, although three to five times the usual intraperitoneal dosage was necessary. Hartman et al; (1932) advocated the intravenous use of extracts only in those patients suffering from a crisis. Grollman and Firor (1935) described a method for absorbing the adrenal cortical hormone on charcoal, thus making it more suitable for oral administration. Later in the same year they reported it successful use, clinically.

Potency

As already mentioned, much rivalry exists to-day among investigators in this field as to the relative potency of their respective preparations. The main discussion centers around the commercialized preparations of Hartman, and of Swingle. Rogoff's "interrenalin" has not been so critically analyzed, probably because it has not been commercially available. Britton (1930) gives a good review of the subject up to that time. He states that the most effective preparations all contained some degree

of adrenalin and that, to be effective, 150 to 300 times the amount of cortex normally present in the animal had to be administered. He was also of the opinion that it had not been proven that indefinitely long survival periods were possible with the extracts in use. He believed the aqueous extract of Swingle and Pfiffner (1931) to be far superior to any extracts yet devised. Pfiffner et al; (1932) commenting on the problem, believed those extracts prepared from whole adrenal glands rather than dessicated cortex to be four to eight times more potent. Britton (1932) had altered his opinion concerning the extract of Swingle and Pfiffner, believing that too large amounts were necessary to produce results. Kendall and MacKenzie (1933) investigating the amount of active principle in the adrenal cortex extracts, found that only a small fraction was obtainable from either of the preparations of Hartman, and Swingle and Pfiffner. In 1934, Rogoff, investigated the therapeutic properties of Eschatin, the commercial preparation of Parke, Davis and Co., which was derived from the original formula of Swingle and Pfiffner. Rogoff found that Eschatin was totally ineffective when judged by the criterion of Pfiffner and Swingle regarding its value in the revival of cats prostrate from adrenal insufficiency. He concluded that it was not yet possible to rely with safety on the manufacture of cortical extracts on a commercial scale, for general use. Biskind (1935) discussing commercial glandular products,

believed that practically all adrenal cortical extracts, prepared up to that time, contained toxic substances and that none of the commercial preparations on the American market possessed much of the life-sustaining principle. Biskind, however, believed that the non commercial preparation of Rogoff and Stewart was as potent, both clinically and experimentally, as any then in use. He concludes that the difficulties attendent with the production of these extracts on a commercial scale have not been surmounted. Grollman and Firor (1935) agreed with Rogoff (1934) that the commercial preparation derived from the original extract of Pfiffner and Swingle was impotent and not suited for clinical usage. In a case of Addison's disease associated with thrombo-angiitis obliterans reported by Silbert (1937), both Eschatin and a recent laboratory product of Swingle and Pfiffner were used. Silbert noted an unusually good effect following the employment of the laboratory extract of Swingle and Pfiffner. This extract was substituted for the commercial preparation (eschatin) which had previously proved ineffective.

In summarizing it may be said that adrenal cortex extracts occupy a rather unsatisfactory position, today, in many respects. Their preparation is difficult and complicated and requires a great deal of cortex material, thus making their commercial production expensive. The present methods of extraction do not seem to be entirely suited to commercial preparation because of

the toxic product contained in the original extraction. It has not been definitely proven, as yet, that adrenal cortex extracts are effective when uncombined with small amounts of adrenalin. The majority of preparations all contain some degree of adrenalin, and it may be this compound that is the reactive principle. The potency of the commercial preparations has been minimized, hence casting their therapeutic application into disrespect.

Adrenal Cortex Hormone

Before considering the therapeutic application of the adrenal cortex extracts previously mentioned, a survey of the possible underlying active principle is indicated, so that the reader will more easily comprehend what is included in the term, adrenal cortex hormone. The isolation, synthesis, and chemical nature of the adrenal cortical hormone is only a recent problem compared to the interval of time in which investigations have been carried on with adrenal cortex extracts. The chemical nature of the cortical hormone has interested few investigators with the exception of Kendall, who has done practically all the work on this problem that is known today. Kendall, however, has made rapid strides in the solution of the problem in the short time he has been working.

Kendall (1930) was the first to make chemical studies on the suprarenal cortex. He reported the presence of a highly

active and strongly reducing substance known as hexuronic acid. He believes this substance capable of inhibiting formation of pigment in any system in which pigment was formed. Kendall even reported a case of Addison's disease which was treated for a fortnight with hexuronic acid. He stated that this patient showed a distinct decrease of pigmentation. He concluded, however, that this substance was unable to keep animals alive after complete extirpation of the suprarenal glands and was probably unable to restore patients with Addison's disease to health. No more work was done on the subject until the first reports on attempts to separate the active principle was made by Kendall and MacKenzie (1933). Working with the cortical extracts which were then in general usage, they came to the conclusion that the active principle was held in the protein fractions through some combination with phosphoric acid. In the same year, Kendall, Mason, MacKenzie, and Myers, reported a method for the separation of the active principle by extraction with acetone in the presence of sulphuric acid at pH about 3. Kendall tentatively suggested β o-hydroxyphenyl-hydroxypropionaddehyde as the chemical nature of the compound isolated. Kendall (1934) considered this chemical investigation to be only partially complete and admitted that much research was still necessary. Wintersteiner, Vars, and Pfiffner (1934) working independently of Kendall, were concerned with

the identification of a crystalline product which invariably obtained from potent preparations of the cortical hormone. They considered it doubtful if the hormone itself would prove to be a nitrogenous compound. Kendall et al; (1935) reported the probable structure to be some form of a trihydroxy aldehyde and the absence of a specific absorption spectra showed the absence of the benzene ring. In the same year these investigators found physiologic and chemical evidence that two factors, A and B, were present in the compound. They believed that factor A produced the essential action of the cortical hormone. The crystalline product, B, however, was considered as essential before product A would influence the concentration of sodium chloride and urea in the blood. They stated that the compound under investigation, in the presence of sodium chloride, possessed all of the characteristic and essential physiologic properties of the most potent extracts of the cortex of the suprarenal gland. In concluding his work in 1935, Kendall considered the most important problem to solve was whether or not the crystalline compound which had been isolated, was in fact the hormone of the suprarenal cortex.

THERAPEUTICS

Having presented the various factors which influence the therapeutic approach to the problem of suprarenal cortical insufficiency, a more detailed discussion of the treatments employed is now possible. It should be kept in mind that the discussion is in no way limited to the therapy of Addison's disease but rather concerns the treatment of suprarenal cortical insufficiency no matter what the cause. Both clinical and experimental data will be presented since the present theory of therapy has been evolved through a study of these two fields of investigation. For convenience of study the use of cortical extracts, the use of mineral salts, and the combined use of both substances will be presented in that order. Some discussion of the rationale of this type of therapy will be presented at the conclusion.

Use of Cortical Extracts

The use of cortical extracts in the treatment of suprarenal cortical insufficiency had its foundation in the work of Rogoff and Stewart(1926). These investigators found the cortices of the adrenal bodies could not be removed without a fatal outcome in the dogs of their laboratories. This made it possible to postulate the existence of an unknown hormone which was essential to life. This investigation also made reasonable the assumption that some form of cortical material would be of

benefit to those sufferers of Addison's disease. Thus the discovery of Rogoff and Stewart was a signal for immediate experimental and clinical studies of the therapeutic possibilities of cortical material.

The first work in this field of investigation was of necessity experimental in nature. Three months following the above publication, Zwemer (1927) stated that he likewise believed the cortical portion of the adrenal complex to be essential for life and that symptoms of adrenal insufficiency were due to removal of the cortex and not the medulla of the gland. To substantiate his statements Zwemer cited some experiments in which the life of adrenalectomized cats was prolonged by transplanted cortex. He believed the prolongation to be due to the resorption of the cortical tissue and its contained hormone. Rogoff and Stewart (1927), utilizing a crude extract of dog adrenals to which they applied the name "interrenalin", increased the survival period of their adrenalectomized dogs. When they employed epinephrine, under similar circumstances, they found no effect on the survival period. This work rather definitely established the cortex as the essential portion of the adrenal gland and gave impetus to the use of cortical extracts in the clinical treatment of suprarenal cortical insufficiency. Hartman, MacArthur, and Hartman (1927) presented their cortical preparation "cortin", which was believed to

contain the essential hormone, and definitely prolonged the lives of adrenalectomized cats. Although Rogoff and Stewart (1928) found a prolongation of the survival period of suprarenalectomized dogs with their cortex extract, the improvement was less striking than in the series treated with Ringer's solution. This latter finding becomes of significance when the use of mineral salts are discussed later. Swingle and Pfiffner (1930) using an extract of their own make, indefinitely prolonged the lives of adrenalectomized cats. At the time of publication, some of the cats had been alive for eighty days. This rather definitely proved, experimentally, that some therapeutic value was contained in cortex preparations when it is considered that the average life span for adrenalectomized cats is twelve days. Hartman (1930) advanced a step further when he found extract therapy not only enabled adrenalectomized animals to survive indefinitely in good health but also to grow. Britton (1930) however, was not so enthusiastic about the benefits of cortical extracts, experimentally. He called attention to the fact that most of the cortical extracts employed up to that time were not entirely free of epinephrine. He was not yet satisfied that indefinitely long survival periods were possible with the use of extracts and that satisfactory proof was necessary to demonstrate the absence of accessory cortical tissue in treated animals. Pfiffner and Swingle (1931) allowed their

animals to lapse into complete prostration by witholding treatment and brought them back to normal health and activity by the employment of cortical extracts. Swingle and Pfiffner (1932) kept cats alive 100 days with their extract and came to the conclusion that there was no such thing as an overdose in the employment of extract therapy. Although subject to the limitations of any experimental work, these investigations indicated some beneficial results could be expected from the utilization of extracts, clinically. These experimental studies also served as a foundation by which the clinical investigations could make a more orderly advance.

The first clinical studies were made by Rogoff and Stewart (1929), who cited seven cases of Addison's disease to prove their assumption that extract therapy was of benefit in suprarenal cortical insufficiency. Seven cases of Addison's disease of varying intensity had been observed by these workers since 1927, and all had received "interrenalin". In only one case was the diagnosis confirmed by postmortem examination, and the fatal result was believed by Rogoff and Stewart to be due to voluntary discontinuance of treatment. The remaining six cases all appeared to show definite improvement under the regime of these investigators. Rogoff and Stewart considered their results promising but believed a much longer period of observation was necessary before the possibilities of permanent recov-

ery were considered. Kendall (1930) making chemical studies of suprarenal cortex found a highly active and strongly reducingsubstance to be present which he considered as hexuronic acid. Treatment of a patient with Addison's disease for a fortnight with this substance, showed a distinct decrease of pigmentation. Kendall concluded, however, that this substance was probably unable to restore this patient to health. Rowntree et al; (1930), using the preparation of Swingle and Pfiffner, brought a patient from the state of collapse back to normal three times during a period of six months. In the interval between the crisis the parient had been put on the Muirhead regime (the administration of epinephrine hypodermically and whole adrenal glands by mouth). The patient had not received continuous injections of cortical extract because of the limited amount available at that time. From the dramatic results in this case, Rowntree and co-workers were convinced of the apparent efficacy of this cortical extract. Rowntree and co-workers (1931) reported a further series of twenty cases of suprarenal insufficiency. Three of these cases apparently received adequate treatment with cortical extract in the opinion of Rowntree and co-workers, but did not do well. Two cases of this group of three were found to have tuberculosis of the suprarenal capsules at autopsy while the other case was found to have adrenal atrophy. They considered the results of this group

found at autopsy. One case was kept alive for nearly eight months by the use of "cortin". That cortin was of benefit was indicated by four definite relapses which followed the reduction or discontinuance of this therapy. This case finally died of a pneumonia. The other case was not considered to have had sufficient therapy. Thompson and Whitehead (1931) reported three cases of suprarenal insufficiency under treatment with cortical extract. The improvement in these cases was very slow and gradual. These investigators, however, considered this type of therapy to be much more satisfactory than the Muirhead regimes previously used on these patients. Harrop and Weinstein (1932) reported a series of nine patients which had been treated with cortical extract for periods varying from three to eighteen months. Of this number there were five deaths, four showing at autopsy marked or complete cortical atrophy, and one bilateral suprarenal tuberculosis. The remaining four patients were maintained in rather good condition although with somewhat restricted activity. Their studies indicated that more favorable results could be expected if treatment was started early in the disease and in patients who have had few or no relapses. Hartman and coworkers (1932) reported an additional six cases, two represented severe stages of Addison's disease and four others presented less severe aspects of the syndrome. All of these were

to indicate that cortical extract treatment is not invariably effective. Of the twenty cases, two cases were in a state of collapse when treatment was started. Both cases died and were found to have bilateral tuberculosis of the suprarenals at autopsy. The results of these two cases are in marked contrast to the report of Rowntree et al; (1930), just previously discussed. Five cases made a partial response to treatment while at the clinic but required nearly continuous treatment following their dismissal. Such cases were unsatisfactory from the standpoint of rehabilitation but the extract therapy was undoubtedly life saving. Of these twenty cases, four made an excellent response to treatment while under care of the investigators, but did not continue treatment at home and died in crisis. No postmortem reports were available on this group of four. Nine cases of this group of twenty made a satisfactory response to therapy and have continued to do so. Rowntree and co-workers considered a course of treatment in the average case to consist of the administration of from 40 to 60cc of extract over a period of from four to ten days. Summarizing the results of these investigators, it is seen that the therapy advised was at best 50% effective. Such results, however, still made the cortical extract therapy the most effective treatment at that time. Hartman and co-workers (1931) reported two cases in which almost complete atrophy of the adrenals was

being maintained in fair health at time of publication with one exception. This latter case died while under treatment of only three days. Rogoff (1932) reported the results of treatment in a group of 21 cases and non-treatment in a group of 12 patients. Of the six patients under treatment in 1929, when Rogoff and Stewart made their first report, one was still alive, having been maintained altogether for a period of $7\frac{1}{2}$ years on the "interrenalin" regime. Of the remaining five cases first reported in 1929, all had died, either of acute exacerbations of the syndrome or secondary infections. The group of twenty-one patients, which had been under treatment, had an average survival period of approximately three years. The group of t twelve cases, which had been under therapy other that extract administration had a duration of life of one year. Rogoff again emphasized that permanent cure should not be expected and believed that early diagnosis offered a much better opportunity for successful therapy. The observations of Rogoff were the first to have the backing of the time factor. Most previous investigators had allowed too short a time interval to elapse between the beginning of extract therapy and their conclusions. Green, Walters, and Rowntree (1933) reported a case of suprarenal insufficiency which was believed to be the first to undergo a major operation while upon extract therapy. The patient survived the operation successfully with adequate pre-

operative and post operative cortex extract.

In 1933, however, other methods of treatment were coming into vogue and the use of cortical extracts, alone, fell into disrepute. Indeed, Hartman (1933) says of his own product Cortin, "In the terminal stages of Addison's disease cortin sometimes fails to bring about recovery." Harrop et al; (1933) in a review of the problem, believed the clinical value of injections of the cortical hormone as a routine treatment during the remissions of Addison's disease had not been satisfactory. They were of the opinion that the chief value of cortical extract was best demonstrated in the treatment of relapses. Kincov, Zillessen, and Rowntree (1934) likewise reported a case in which treatment with cortical extract was relatively ineffective after the initial administration.

Reviewing as a whole the investigations which employed the cortical extracts as the sole therapeutic measure in cases of suprarenal cortical insufficiency, the results were not the most desireable nor were the extracts dependable as therapeutic measures. This type of therapy, however, did represent a definite step forward in that it was much more satisfactory than the previously employed Muirhead regime. With the advent of newer methods of treatment and more modern investigations, the value of cortical extracts was gradually deemphasized until this form of therapy was considered as a necessary adjuvant to successful treatment rather that a panacea for

cortical insufficiency.

Use of Mineral Salts

The type of therapy which was destined to supersede the use of cortical extracts had its basis on the experimental work of Stewart and Rogoff (1925). These workers observed an increased survival period of adrenalectomized dogs maintained only on Ringer's solution. Corey (1927) observed that solutions of certain substances such as glucose and sodium chloride were more effective than others in maintaining their animals in a normal condition following bilateral epinephrectomy. Like Stewart and Rogoff, Corey believed these fluids to be merely pallitative measures rather than curative and could in no way substitute for the missing hormone. The real clue to the problem came, however, from the work of Marine and Baumann (1927). These authors experimented with several cortical preparations of their own making as possible agents to maintain the life of their adrenalectomized animals. Using the duration of life as the test, their results indicated that certain preparations prolonged life but that the degree of prolongation might as well have been due to the water and sodium chloride injected with the extracts as to any substance peculiar to the extracts. Indeed, they say, "Administration of physiological salt solution alone caused an average higher duration of life than the cortical extract". As an afterthought they surmised the sodium ion might also have a more specific action

in prolonging life than simply offsetting acidosis. Rogoff and Stewart (1928) publishing a series of observations on adrenal insufficiency, observed many of the facts which were to be found in the work of Marine and Baumann (1927). Rogoff and Stewart observed a marked prolongation of the survival period in their adrenalectomized dogs by the daily injection of Ringer's solution. They also noted a marked amelioration of symptoms, even when acute, following these injections. Although a similar series of animals were treated with cortical extract, the results were less striking than the series to which Ringer's solution had been administered. These investigators, however, considered the salt solution as an adjuvant to the use of cortical extracts in the treatment of cortical insufficiency, since the salt solution could not substitute for the missing hormone. They considered the use of salt solutions to be indicated in those cases where it was necessary to wash out of the body system the accumulated toxins, thus allowing the hormonal extracts to exert a better influence. They also considered salt solutions as valuable in the therapy of crisis. In spite of these postulations which tended to emphasize extract therapy, they admitted, "To our own observations the Ringer treated animals even seemed to survive longer than the extract treated". Unlike Marine and Bauman, Stewart and Rogoff made no suggestion concerning the possible influence of the sodium ion alone. The latter investigators also tended to

deemphasize the real results of their experimentation in favor of the more theoretical treatment. If Rogoff and Stewart had given more emphasis to the beneficial effects of salt solutions, much of the overemphasis given to cortical extracts in the following years would have been prevented, since the opinion of these authors carried considerable weight at this time.

Although the results of the above investigations, especially those of Marine and Baumann, and Stewart and Rogoff, indicated that a partial benefit could be obtained by the use of solutions containing mineral salts, the therapeutic possibilities of such solutions were disregarded in favor of the theoretical treatment. The work of these authors was forgotten in the years to follow, and all investigative work was engaged in perfecting cortical extracts for use clinically and for commercialization. Approximately six years following the work of Stewart and Rogoff, investigators once again turned their attention to testing various solutions as possible aids in the therapy of cortical insufficiency. In the interval which had elapsed, cortical extracts had not proven to be the sole answer to the problem. Rubin and Krick (1933) were among the first investigators to recall the upset of calcium, sodium, potassium, magnesium, chloride, and nitrogen balances following adrenal ablation. These authors made a mixture of 0.03% $CaCl_2$, 0.01% $MgCl_2$, 0.7% NaCl, and 0.03% KCl. They observed a marked improvement in the adrenalectomized animals

to which this mixture was administered.Even if this solution was not administered until within two or three hours before the time of death would have ordinarily occurred, the animals were restored to a normal state within five hours. Administration of this solution alone kept their animals alive for at least four months. The results following the employment of normal salt solution were less striking than with the above mixture. Swingle and co-workers (1934), however, found that injections of normal saline solution equal in amount to the cortical hormone given, were without effect on the symptoms of experimental cortical insufficiency. Zwemer (1934) found that certain amounts of sodium chloride by mouth were effective in prolonging the life of adrenalectomized cats.Zwemer was of the opinion that sodium salts would be of great benefit clinically in those cases of partial insufficiency in which some active cortico-adrenal cells were still present. He did not believe sodium chloride to be a cure for adrenal insufficiency but rather a necessary adjuvant to extract therapy. Gaunt, Tobin, and Gaunt (1935) believed the general finding for salt treatment, expreimentally, was a prolongation but not an indefinite maintenance of life. Harrop et al; (1935) reported a group of experiments in which suprarenalectomized dogs were maintained in apparently normal condition for a period of five months without the use of any suprarenal gland preparation and by the administration of sodium chloride

and sodium bicarbonate alone. Withdrawal of these salts produced the typical symptoms of adrenal insufficiency. Harrop et al; (1935), however, did not believe the dogs could be indefinitely maintained on such a mixture but injections of cortical extracts would be necessary to enable the animal to maintain the salt balance. Thus it may be observed that the trend of thought included a combination of both cortical extract and salt solution as the proper therapeutic measure for suprarenal cortical insufficiency. Kendall (1935) added further to this postulation by showing that adrenalectomized dogs could not be maintained adequately when either salt or cortical extract alone were administered, but when combined the result was striking. Richter (1936) showed that the salt appetite of adrenalectomized rats was markedly increased, and if this appetite was satisfied, the survival rate over those on a salt free diet was markedly prolonged.

With the advent of experimental studies on the use of salt solutions in 1933 and disregard for administration of cortical extracts clinically, clinical observations on the employment of salt therapy began to appear. Among the first to make such observations were Harrop and co-workers (1933). These men considered the clinical value of injections of cortical hormone as a routine treatment during the remissions of cortical insufficiency, to have proven very unsatisfactory up to that time. In their opinion the chief value of the extract therapy was to be found

in the treatment of the relapse. They reported four cases of hormone insufficiency which were maintained in a very satisfactory manner by the simple administration of from one to six grams of sodium chloride daily in addition to high salt content diets. These cases were maintained in this manner entirely free from extract injections except during periods of relapse as the result of intercurrent infection. Snell (1934) likewise believed salt therapy to be an indispensable adjuvant to the therapy of Addison's disease and that its administration greatly reduced the need for hormonal extracts. In contrast to Harrop (1933), Snell believed the salt therapy to be more useful in the treatment of crisis rather than the remissions. Blankenhorn and Hayman (1935) pointed out the failure of cortical extract, alone, to prevent the development of crisis. They reported a case which was maintained for a period of four months in fair condition by sodium chloride alone, without cortical extract. When the patient was first seen, an extreme suprarenal insufficiency crisis existed. These authors also found that other sodium salts could be substituted for the chloride salt without detriment. The amount of salt administered in this case was twelve grams daily, almost twice the amount utilized by Harrop (1933). Although the above investigations strongly emphasized the usefulness of salt therapy, the work was modified in large measure by the series of publications by Kendall (1935). This author administered twelve to fifteen grams of sodium chloride to a

patient daily but failed to prevent the appearance of acute symptoms of adrenal insufficiency. Grollman and Firor (1935) likewise believed the remedial effects following the use of sodium chloride alone were only temporary, and like other useful forms of therapy these were incapable of supplying the need for the adrenal cortex hormone.

When all conclusions as to the proper therapeutic approach to suprarenal cortical insufficiency are considered, it is difficult to decide just what treatment is indicated. The variance of opinion among the investigators cited above, certainly does not justify making a definite conclusion. Although up to the year 1933 cortical extracts were considered to be specific for this condition, their usefulness has since been minimized. Sufficient beneficial effects resulted from their usage, however, that cortical extracts must be included as a part of the ideal treatment. In a like manner the use of solutions of mineral salts were emphasized, but recent investigations indicate they are incapable of maintaining in a satisfactory condition patients suffering from cortical insufficiency. The obvious question which occurs in the reader's mind is, just what treatment should be employed?

Combined Use of Mineral Salts and Cortical Extracts.

The solution to this question was found when the two methods of therapy were combined. Support for such a possibility is to be found both experimentally and clinically. Although they did

not necessarily advocate the combined type of therapy, Rogoff and Stewart (1928) and Zwemer (1934), when they really wished to prolong the lives of their experimental animals, employed both cortical extracts and salt solutions. Clinical observations such as were made by Rogoff (1932), Hartman and co-workers (1932), and Snell (1934), proved the remissions from symptoms of insufficiency were more lasting when both types of therapy were combined. It was not until the time of Kendall (1935), however, that this form of therapy was strongly advocated. This worker found that neither experimental animals nor human subjects progressed satisfactorily when cortical extracts or salt solutions alone were prescribed. When the two methods were combined, however, the results were striking. At the present time the majority of investigators, who were formerly opposed to one another as to the respective merits of a particular treatment, consider the combination of both cortical extracts and sodium chloride to offer the most satisfactory therapeutic approach.

Nevertheless, certain cases of insufficiency failed to progress satisfactorily even on this type of therapy. On several occassions it was noted that certain cases of severe Addison's disease developed insufficiency in spite of an adequate intake of sodium chloride and liberal use of a cortical hormone of proved potency. It remained for Wilder, Snell, Kepler, Rynearson, Adams, and Kendall (1936) to point out another factor which had

heretofore received scant attention. Working on the proven fact that an increase of serum potassium existed in patients suffering from cortical insufficiency, they found that ingestion of a certain amount of potassium produced a sharp decrease in serum sodium and plasma chloride with the appearance of insufficiency symptoms. This was found to be true even though the diet contained a liberal amount of sodium chloride. Clinically, if the intake of potassium was no higher than that provided by an ordinary diet (4 grams or more) even generous quantities of sodium salts (18 grams of NaCl) would not prevent the development of crisis. These authors cited three cases which were maintained in good condition by the administration of sodium salts only, providing the intake of potassium was restricted. These cases had previously required the administration of cortical hormone. One patient was maintained for seven days without difficulty on a diet restricted in sodium salts, while subsisting on a diet low in potassium. These workers considered the ideal diet for cases of cortical insufficiency to include 1.6 grams of potassium or less and at least 16 grams of sodium chloride daily.

Physiology

To attempt an explanation as to how these various forms of therapy induce beneficial effects in patients afflicted with cortical insufficiency, is indeed difficult. As each form of treatment was evolved, certain theories were postulated to explain the basis for their effect. Stewart (1929) commented on

the newly discovered remedial effects of intravenous salt solutions. He explained their beneficial effect as due to the neutralizing action on toxic products, which accumulated in the body system during cortical insufficiency, thus aiding the action of cortical extract administration. Swingle and Pfiffner (1932) were of the opinion that cortical extract administration made possible a restoration of kidney function, thus allowing for the normal excretion of metabolites which were known to accumulate in the blood stream during insufficiency. Hartman (1933) was not quite so specific in his explanation. This author believed the cortical hormone to be simply a general tissue hormone. He considered the beneficial effects attendant with its administration to be due to its importance as an essential body component. As for the administration of salt solutions, he considered these as aiding in the restoration of the water exchange of the tissues. Zwemer and Sullivan (1934) considered the cortical hormone to be intimately related to the ability of the body cells to metabolize salts and water, Harrop and co-workers (1935) correlated sodium chloride administration as a factor in the restoration of the plasma chloride level. When the plasma chloride was restored, the secretion of hydrochloric acid in the stomach was again possible, thus relieving the distressing symptom of anorexia. These authors considered the suprarenal cortical hormone as probably concerned with the regulation of sodium excretion by the kidney, and thus eventually with the proper mainten-

ance of water balance in the organism. In 1936 these same authors correlated the beneficial effects of suprarenal cortical hormone administration as due to the large amounts of potassium excreted by the kidney. The rationale of the treatment advocated by Wilder, Snell, Kepler, Rynearson, Adams, and Kendall (1936) was not quite so theoretical in nature. These authors were aware of certain proven fundamental facts, which were known to occur during insufficiency, and regulated their therapy accordingly. The potassium was kept low in the diet because it was known to increase during insufficiency. The sodium and chloride salts were administered freely because decreases of these salts were evidenced during insufficiency. The cortical hormone was also administered because it was certainlly partially absent. Although such an explanation is still unsatisfactory in many respects, the work of these authors represents a logical attempt to restore all possible abnormal factors to normal. When the numerous other possible factors concerned with mineral metabolism are considered, it is impossible to offer a logical explanation for any particular type of treatment until the logical therapy, itself, is worked out.

SUMMARY

In summarizing the problems of suprarenal cortical insufficiency, certain salient features are prominent in the progress of the investigative work to date:

1. Isolation of the suprarenal cortical hormone in the crystalline form and discovery of the true chemical nature of this hormone is not far distant.

2. Partial absence or lack of secretion of the cortical hormone is apparently associated with profound alterations of water and mineral metabolism. The importance of the cortical hormone as an essential feature in the maintenance of life and as a general tissue hormone must also be recognized.

3. Commercial cortical extracts must be improved before the acme of perfection, from a therapeutic standpoint, is reached.

4. The symptomatology of suprarenal cortical insufficiency remains unexplained on the basis of the postulations as to the fundamental physiological disturbances which occur in this syndrome.

5. The therapy which is theoretically sound and is apparently beneficial, combines the use of cortical hormone preparations as an adjuvant to increased sodium and chloride salts, and decreased potassium salt consumption.

6. From the therapeutic aspect, the symptomatic relief of suprarenal cortical insufficiency is still not entirely satisfactory. Many other factors still remain to be considered. The

possibility of an upset in calcium metabolism and an interrelationship between the adrenal cortex and parathyroid glands are to be considered. The entire endocrine balance and the relationship of other glands of internal secretion to the adrenal cortex must also be taken into account. In the last analysis it must also be remembered that 80% of the cases of suprarenal cortical insufficiency are associated with tuberculosis, which, alone, is a distinct therapeutic entity.

ADDITIONAL FACTORS RELATED TO THE PROBLEM

Before the discussion of the problems of suprarenal cortical insufficiency is complete, mention of the additional possibilities in the therapeutic use of the cortical hormone is necessary. When cortical extracts were first found to give beneficial results in cases of Addison's disease, The hormone elaborated by the adrenal cortex was immediately considered to be a panacea for many ills. An enormous amount of investigative work was undertaken to test the therapeutic possibilities of this hormone in almost every disease entity. From these investigations practically nothing of present day value has been derived. As the cortical hormone was found to be less specific in the treatment of Addison's disease, cortical hormone therapy in other fields was likewise minimized. At the present time cortical hormone therapy is employed in only a few fields.

It has been rather definitely known for about three years, that some relationship existed between the suprarenal cortex and vitamin C. Svirbely and Kendall (1936) called attention to this relationship because of the constant presence of ascorbic acid in the suprarenal glands of normal animals. At the present time the suprarenal cortex is believed to be only a storage depot for this acid. Wilson, Rowley, and Gray (1936) called attention to the usefulness of cortical extracts as an adjuvant to the treatment of burns. They considered the hormone to be beneficial in combatting the acute toxemia which results from

burns. In the field of obstetrics Freeman and Melick (1935) have reported the successful use of cortical hormone in the treatment of pernicious vomiting of pregnancy. Cohen and Rudolph (1936) considered the possibility of cortical hormone as a substitute for epinephrine in the treatment of asthma. The hormone was found to have little significant effect. Of all the claims as to the beneficial effect of cortical hormone therapy, the most striking is the one reported by Coffey and Humber (1936). They reported the use of an aqueous extract of suprarenal cortex in 7,513 cases of inoperable and hopeless malignancies. At the end of five years a review of the results of treatment revealed 10% of the cases still living.

To make conclusions as to the benefit of cortical hormone in conditions other than those which result from insufficient function of the suprarenal cortex is impossible. The investigative work must stand the test of time.

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