Vital hormone of the suprarenal cortex and adrenal insufficiency

Maxwell T. Wainwright
University of Nebraska Medical Center

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THE VITAL HORMONE OF THE SUPRARENAL CORTEX

and

ADRENAL INSUFFICIENCY

by

MAXWELL T. TAINWRIGHT

Presented
to The Faculty of
The University of Nebraska
College of Medicine.

Omaha, Nebraska.

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Introduction
THE VITAL HORMONE OF THE SUPRARENAL CORTEX
and
ADRENAL INSUFFICIENCY

The adrenal glands were first described by Eustachius in 1563, but up till the middle of the nineteenth century, they were chiefly objects of curiosity to anatomists and excited little interest among members of the medical profession. Not until Addison's description, in 1855, of the disease which bears his name, did these glands come into prominence. (1) He attributed the malady to a diseased condition of the adrenal cortex, for in his definition, he says, "the leading and characteristic features of the morbid state to which I would direct attention are anemia, a general languor and debility, a remarkable feebleness of the heart's action, irritability of the stomach and a peculiar change of color of the skin occurring in connection with the diseased condition of the suprarenal capsules."

Since this classical work of Addison's, the adrenal glands have played a prominent role in the speculations and theories of biologists and clinicians, even though one of a doubtful nature.

The therapeutic measures used against Addison's disease up till recent years have been purely symptomatic. Osler, (46) in his treatment of the disease, gives no reference whatever to organotherapy. Rowntree and his associates (53) introduced a
treatment for the disease in which he used epinephrine to the tolerance of the patient along with desiccated adrenal cortex or whole gland by mouth. His results were good in some cases, while others received little or no help. As early as 1895, whole gland therapy was used by George Oliver. He reported a case of Addison's disease which received an alcoholic extract of suprarenal gland. The case was followed over a period of eight years, given an occasional injection, and reported as doing well, however, such success did not attend all of his attempts at organotherapy.

With the use of the Muirhead treatment, instituted by Rowntree, some success has been reported. In this type of treatment, the benefit was probably from the amount of cortex or whole gland used and not from the epinephrine, as witnessed from experiments with the new extracts prepared from the adrenal cortex. Here it was shown that the use of the extracts was limited, due to the amount of epinephrine in them, and not until it was removed, could sufficient doses of the cortical extract be used.

Up till the time of isolation of the vital hormone of the suprarenal cortex, the Muirhead treatment was in favor in most all clinics, along with other symptomatic measures. This treatment was only partially satisfactory, and undependable and hence lead to the investigation and isolation of the new hormone. As is seen, by looking back over a period of years, the presence of a "vital factor" in the adrenals has been suspected for some time, but not until such investigators as Swingle and Pfiffner (64), Hartman and Brownell (34), Stewart and Rogoff (51) and others were attracted, was there a successful attempt made at isolating the hormone.
Since Addison's disease is the characteristic clinical entity of insufficiency of the adrenal cortex, the development of its treatment parallels closely the investigative efforts made on the adrenal gland. It has been made evident by innumerable experiments that adrenalin is not the underlying cause of Addison's disease, but that some other factor, which is of vital importance to existence, has to do with that malady.
PART I

The Preparation of the Adrenal Cortical Hormone.
The Preparation of the Adrenal Cortical Hormone.

Considerable difficulty arose in isolating the hormone of the cortex without having too much epinephrine present to make it unsuitable for use. Not until in October, 1927, were there reported any experimentations with extracts. Stewart and Rogoff, at that time tried to isolate the hormone by the use of (1) isotonic salt solution and (2) by a glycerol extract of the cortex. By this extraction method, however, there was so much epinephrine present, that intravenous use was impossible, and intramuscular use difficult.

During the same month, Hartman, et al, (34) reported several methods that had been tried in an effort to isolate the hormone, and tested it experimentally on laboratory animals for its potency—the ability to maintain the lives of adrenalectomized animals. The difficulty arose in removing the epinephrine without injuring the cortical hormone.

The extracts of Hartman, et al, (34) were prepared from fresh beef adrenals which had been obtained from a packing house. The glands were immediately chilled by putting them in an iced conveyor to be transported to the laboratory, where they were prepared for extraction. This consisted of a careful and tedious dissection of the cortex from the medulla of the gland which contained the bulk of the epinephrine. It was thought that by this means, a large percentage of the epinephrine would be disposed of.
After the cortical portions had been separated, they were ground in a mortar or chopper till very fine, then shaken for fifteen to thirty minutes with three times their volume of distilled water. At this point, one-tenth normal acetic acid was added to make filtration more rapid. The filtrate from this served as the starting point for all their methods of preparation. It had an acid reaction, about a pH 4.4 to 4.9, and one cubic centimeter of the solution equalled the substance from 0.2 gram of the cortex. This still contained all of the epinephrine, and the next step was to free the hormone from it. Hartman and his associates tried eight methods and slight variations of preparations. One method was by oxidation, the use of potassium permanganate added drop by drop until the epinephrine was all destroyed. Another method was by shaking the acetic extract with weighed charcoal. Again he tried dialyzing the acetic extract against a large volume of isotonic salt solution through a collodion bag for eighteen to twenty hours. Another method of dialysis worked on the possibility that the hormone could pass through a thin collodion membrane easier than it could through a thick membrane. The extract for injection was prepared, then, by placing the aforementioned acetic extract in a small, thin bag of collodion which was in turn immersed in a larger, thick bag of collodion which was filled with isotonic salt solution (0.9%). The combined sacs were then immersed in a large body of isotonic salt solution. These were allowed to dialyze for a period of eighteen hours, then the extracts removed. It was found by animal injection that the solution coming from the outside small bag and inside the large bag was the most potent.
By the use of these extracts on adrenalectomized rats, it was found that the extracts prepared by the latter three methods were the most potent and efficient. The rats were kept well and in good condition, some as long as eighty days, these dying from the symptoms of insufficiency because the extract was discontinued.

Not satisfied with the extracts prepared, Hartman, et al (34), tried using hydrochloric acid in preparation of the fresh gland. It was prepared in exactly the same manner as the acetic extract, except that the hydrochloric acid was substituted for acetic acid. This method, however, did not yield as potent an extract as with acetic acid.

Another method tried by Hartman, was shaking the pulp of the cortex with two volumes of water and then filtering. This was then dialized for nineteen hours at a cold temperature against a large volume of distilled water. To the residue remaining, 1.4 cubic centimeters of normal hydrochloric acid was added to every 100 cubic centimeters and again dialized. This final product was neutralized and used for injection.

Still another method similar to the one just above was tried. In this method, nine cubic centimeters of normal hydrochloric acid was added to every 100 cubic centimeters of extract, (acetic), and then dialized against acidulated water. The end product was neutralized to pH 7.4 to 7.6 and used for injection. This last maneuver was intended to remove the epinephrine. In further experimentations, he used charcoal to separate the epinephrine instead of dialysis; and also the use of five cubic centimeters of normal hydrochloric acid per 100 cubic centimeters of extract (acetic) and letting stand for 30 minutes before dializing against
equal volumes of 0.9 % sodium chloride through collodion. These methods were not successful for they allowed the extract to stand too long resulting in a loss of potency.

Further methods tried by Hartman, et al (34), were by precipitation and by supracentrifugation. In the precipitation method, several variations were tried. One consisted of adding enough trichloracetic acid to the acetic extract to produce a precipitate. This was washed and redissolved in water and then sodium hydroxide was added to carry it into solution. Sodium chloride was added to bring the extract to isotonic concentration.

Another trial was by saturating the acetic extract with sodium chloride to form a precipitate. This was washed with a saturated solution of sodium chloride and then filtered by gravity. The precipitate was dissolved in water so that one cubic centimeter of the extract would equal the yield from one gram of cortex. Hartman made a few variations from this, in one series, by adjusting the sodium chloride content to 0.9 % and the pH of the final extract to 7.0. In another series, he dissolved the sodium chloride precipitate in only one-half the usual amount of water and dialized it through a collodion bag against a 0.9 % sodium chloride solution by shaking. If the collodion membrane was completely permeable, one cubic centimeter of the final extract equalled the yield from one gram of cortex. In another series, he did a third precipitation in an attempt to purify the extract. The pH was adjusted to 5.4 in preparation for saturation. The solution was filtered by gravity. At each precipitation, the precipitate became less and less soluble.
His final trial at preparation of extract in this series was by the use of a high speed centrifuge in the place of the slow filtration method. He found that much of the potency of the extract was lost when it was allowed to stand in the precipitate for long periods of time. The same acetic extract was used as before described, and it was salted out by the use of sodium chloride. Also, he tried further purification of the extract by a second precipitation. The extract of the first precipitation was dissolved, reprecipitated and again centrifuged. In this series, one cubic centimeter of the extract equalled five grams of the cortex.

On a final comparative analysis of the potency of all the extracts prepared by these methods devised by Hartman, et al, it was found that by the use of the precipitation methods, as more potent substance was obtained. He reports having kept animals alive for eighty days. The value of controlling the pH of the solutions and the sodium chloride content was brought out by an increase in the life expectancy of animal of almost ten days. The supracentrifuged specimens gave the best results; by its continued use he kept an adrenalectomized cat alive for eighty days, death ensuing after withdrawal of the extract.

Since these are among the first experiments tried at isolating the cortical hormone, Hartman, Brownell, et al (34), have produced sufficient evidence that the adrenal cortex does produce a hormone that is vital to life. Here they propose the name "cortin" for the product. They had contemplated the name "corticin" but there is a product from the bark of the populus tremula by that name and would lead to confusion.

In 1928, a German author, Goldzicher (22), also reported the isolation of a hormone from the adrenal cortex which pro-
longed the life of adrenalectomized rats. The method of extraction is given as being the same as that for the isolation of insulin. The active principle obtained in this method is a white, amorphous powder which is soluble in dilute acids and alcohol, but insoluble in water, weak alkalies, ether and chloroform. This product, as analyzed by the author, has an antagonistic action to adrenalin, in reference to blood pressure. This product produces a fall, while adrenalin produces a rise. This does not conform with the effects of the hormone produced by American authors. The product is said to increase the life expectancy of adrenalectomized rats to eighty days while untreated rats lived only fourteen days.

In 1930, Koeler and Eichelberger (41), reported the separation of an epinephrine-free substance from the suprarenal gland which elevates the metabolic processes and improves clinical asthenia. The preparation of the substance, the authors claim, depends on the separation of epinephrine and other substances such as choline and finally concentration by removal of inactive substances. Two methods of preparation have been reported by these authors. The first is a method where the active principle is carried down by a protein precipitation. In this method, a aqueous extract of the fresh gland is adjusted to pH 4 or 5 with acetic or other non-oxidizing acid, and the protein is precipitated by three-quarter saturation of sodium chloride. The precipitate can be washed free of non-combined epinephrine. Such precipitates have a depressing effect on the metabolic rate and give an unfavorable clinical action. If it is left to stand and protected from oxygen, it lose its depressing effect and raise the metabolic rate. This change is best accomplished by heating it with hydrochloric acid on a water bath for ten
to fifteen minutes. The active principle can be separated from the protein bulk by drying the acid solution in vacuo so as to remove the moisture and then extracting with absolute methyl alcohol. The extract is adjusted to pH 4.5 with ammonia, then is precipitated by adding seven volumes of acetone. To make a more purified extract, the precipitate is redissolved in alcohol and again precipitated with acetone.

The second method suggested by Koehler and Eichelberger (41) was a lipoid method. The fresh beef glands were extracted with an alcohol-ether mixture, starting with an 80 percent methyl alcohol and 20 percent ether, and gradually reversing the reaction on subsequent extractions. The alcohol-ether solution is distilled off in vacuo and the water-lipoid residue is extracted with ether. The extract is washed with water and then dried over sodium sulphate in a dessicator and the ether evaporated. The residue is treated with absolute methyl alcohol containing dry hydrochloric acid gas and then heated on a water-bath for fifteen minutes. The pH of the alcohol solution is adjusted the same as in the former method and precipitated by acetone. Purification is carried out by redissolution and precipitation. The physiological effects on adrenalectomized cats and the potency of the two is quite similar.

Further reports on the isolation of the cortical hormone were made in March, 1930, when Swingle and Pfiffner (68) had prepared a lipoid extract. This was their first attempt at extraction, and involved a long, drawnout process, but they had a highly potent extract. Two difficulties arose with this extract; it had an oily base and could not be used intravenously for emergencies, and it produced an abscess at the point of repeated injections;
and its epinephrine content was so high that only small doses could
be used without producing a reaction. In preparing this extract,
fresh beef glands were used. These were stored in ice until ready
for use, always within twenty-four hours after killing. The extra-
fat and connective tissue was removed from the gland and the cortex
was dissected free from the medulla. The cortex was extracted for
twenty-four to seventy-two hours with two and one-half volumes of
95 percent alcohol, being stirred occasionally. The alcohol was
then removed by straining through muslin and filtering. The residue
was pressed dry and extracted with two volumes of 80 percent. ethyl
alcohol for from one to three days. This was again removed by strain-
ing and filtering, and the filtrates from both extractions were then
concentrated to one-fifteenth their volume by heating to 50 to 60
degrees Centigrade. The concentrates were mixed with equal volumes
of benzene and set aside in a refrigerator. The benzene solution
of lipoids was removed later and the aqueous residue again extracted.
The benzene washings were combined and the benzene was removed in
vacuo at 45 to 50 degrees Centigrade. The last trace of the benzene
was removed by 50 to 100 cubic centimeters of absolute alcohol and
distilled to dryness. The lipid residue was taken up with olive oil
or corn oil for injection with the aid of absolute alcohol. The
alcohol was again removed by distillation. Enough oil was added to
the lipid residue so that one cubic centimeter equalled 30 grams of
cortex. The extract was stored at 6 degrees Centigrade until needed.
This extract contained about two milligrams of adrenalin per cubic
centimeter. Even though there was still enough to give a marked
physiological effect, about 96 to 97 percent. of it had been re-
moved.
The next communication on the preparation of an extract was that of Hartman, Brownell and Hartman (33), in which they have succeeded in eliminating almost all of the epinephrine. They have experimented with the use of sodium chloride as a precipitant, but they find that much of the potency is lost by this method. They also attempted heating the extract to precipitate proteins but found that the hormone is destroyed by this method. A new method, one by extraction with solvents, has proved more satisfactory. They use of ethyl ether, and believe it to be the best. Here one or two volumes of ether is added to the minced fresh whole gland in a closed vessel and the air is replaced by carbon-dioxide. The mixture is shaken for 24 hours, and the ether changed. This is repeated two or three times. The ether from these extractions is then combined and filtered, and the ether removed in vacuo. The ether is extracted three times with 80 percent alcohol at 40 degrees Centigrade, and then cooled to a temperature of 45 degrees. The residue is then taken up by 80 percent alcohol, chilled, filtered and distilled to dryness. The residue is taken up by a small volume of ether and the insoluble material discarded. The ether is removed and the residue again extracted but with water to make the desired concentration. The extracts have been made to such concentrations that one cubic centimeter equals the yield from fifty grams of cortex. With this extract, Hartman, et al (33), have kept animals alive indefinitely.

Hartman, et al (30), reported again in 1931, a new method of extraction where they used the cortex of the gland only. The content of the cortical hormone in the medullary portion has been found to be nil, and by using the cortex only, much adrenalin is omitted. It was found also, that the medulla contains much
toxic material, and in an attempt to wash it out, much of the potency of the extract was lost. This latest method of extraction consisted of adding peroxide-free ethyl ether as soon as possible to freshly ground cortex. Four liters of ether was added to three kilograms of tissue in a twelve liter flask. The air in the flask was replaced by carbon-dioxide and the contents agitated slowly. The ether was then poured off and a second and third extraction made. The three were combined and concentrated in vacuo to nearly dryness. The ether was then poured off and a second and third extraction made. The three were combined and concentrated in vacuo to nearly dryness. The residue was extracted four times with 95 to 98 percent ethyl alcohol and heated to 45 to 50 degrees Centigrade. The solutions were kept warm during the entire extraction so that fatty material was kept fluid. For one kilogram of gland, 50 to 60 cubic centimeters of alcohol was used in each extraction with one hour of shaking. The flask was cooled by cracked ice and the alcohol separated, then all the fractions combined. Enough water was added to make the alcohol content 80 percent, the solution chilled to a -10 degrees Centigrade and filtered in a cold atmosphere, (4 degrees C.) removing the undesirable material. This step was very important. The alcohol was removed and the residue extracted with a 60 to 75 percent alcohol, then chilled and filtered. The alcohol was again removed and the residue extracted with a small volume of ether. The ether was driven off by slight heat and the residue again taken up with enough water to make the desired concentration, and sodium chloride added to make the solution isotonic. After passing through a Seitz filter, the extract was ready for injection. This extract had the desired potency and was free from toxic products, but the adrenalin content was still high enough to give a physiologic effect, as determined by blood pressure rise.
R. L. Zwemer (80) reported an extract which he and his associates produced in 1931. This he called "adrenin." His method of preparation can best be shown graphically, as he has shown it in his report. (Figure I) By animal experiment, the author has been very successful in keeping adrenalectomized animals alive, and has shown great improvement in the recovery of animals near insufficiency extremis.

Also in 1931, Swingle and Pfiffner reported a series of experiments with the preparation of new extracts of the cortex (69)(70)(71)(66). The first extract which they prepared was a lipoid extract, and due to abscess formation at the site of repeated injection, its prolonged use was prohibited for the animals became toxic and died in many cases. They saw the need for a more desirable extract to handle, and the second report was of an aqueous preparation. This new extract also gave a more consistent yield and was more pure. The method of extraction was quite complicated and a long process.

In this method (69) the dessicated cortex was finely ground and mixed with two and one-half volumes of 95 percent alcohol and macerated at room temperature for a period of three days. This was strained through muslin and the residue was expressed in a tincture press. The strained fluid was filtered through soft paper and the gland residue reground and extracted the same as the first extraction. The two alcohol fractions were then concentrated separately in vacuo at 50 to 60 degrees Centigrade to one-fifteenth their original volumes. Each fraction was transferred to an equal volume of benzene in a cylinder, mixed, and set aside in a refrigerator to settle. All the extract that was not needed was left in
Preparation of Adrenal Cortical Extract.

Figure I: Preparation of Adrenal Cortical Extract. (Zwemer, Agate, Schroeder, 30)
this state and stored in a refrigerator. This preserved the potency of the extract until needed for future use and then extraction was completed.

The benzene was removed by repeated washing two or three times, as necessary. All the washings were combined and the fluid removed by distillation in vacuo at 45 to 50 degrees. A brown, semi-solid residue resulted. To this residue, 500 cubic centimeters of acetone was added and rubbed, then set in the refrigerator for 24 hours. The acetone was decanted and the residue re-extracted. This last procedure was repeated and the residue put in a mortar and rubbed with fresh cold acetone. This was removed in vacuo at 45 to 50 degrees and again a residue obtained. The residue was transferred to a separatory funnel with 30 cubic centimeters of petroleum ether, 74 cubic centimeters of 95 percent alcohol, 26 cubic centimeters of distilled water and mixed. The resulting 70 percent alcohol was washed with 30 cubic centimeter portions of petroleum ether.

The petroleum ether solutions were then returned to the original flask and the ether removed in vacuo. These distribution procedures were repeated. The petroleum ether from the second distribution was run into a separatory funnel and 74 cubic centimeters of 95 percent alcohol and 26 cubic centimeters of water were added. A petroleum ether solution from a third distribution was similarly treated and also a fourth distribution. The alcoholic solution was washed successively five times with 30 cubic centimeter portions of petroleum ether in the order of second, third and fourth distributions. The alcoholic solutions of the third and fourth distributions were then washed twice with fresh portions of ether. The order of distribution and washing had to be done in the proper succession and done properly or stable.
emulsions were encountered.

The alcoholic solutions were combined and the alcohol removed in vacuo at 45 to 50 degrees, until a volume of 65 cubic centimeters was reached. Water was then added to make 100 cubic centimeters so that one cubic centimeter of the extract equalled the yield from 30 grams of fresh cortex. The extract was left to stand overnight in a refrigerator, then centrifuged, decanted and filtered through a Seitz filter. Here they got a reddish-brown extract with a pH of about 5.2. Each cubic centimeter of the extract assayed about 0.38 milligrams of adrenalin. This content was still quite high and gave a reaction upon injection of large doses. This was cut down very markedly by making only one alcoholic and one acetone extraction and one distribution, but the cortical hormone yield was equally lessened.

In Swingle and Pfiffner's second communication in 1931, (70), they recognized the fault with their first aqueous extract, even though it would prolong the lives of adrenalectomized cats, it could not be administered intravenously in a crisis. They reported a method which was only a slight variation from the former, but the adrenalin content was so lowered that the extract could be administered intravenously, intraperitoneally or subcutaneously.

In this method, the 70 percent alcohol soluble solution was prepared by the same method described in the previous report (69). Three kilograms of cortex were generally used. This alcohol solution contained 1.49 grams of solids and 0.36 milligrams of adrenalin. The solvent of the solution was removed in vacuo at 45 to 50 degrees Centigrade and at the end of distillation a small quantity of absolute ethyl alcohol was added to remove the rest of the water. The residue was taken up with 100 cubic centimeters of 95 percent ethyl
alcohol and the solution filtered through two to 30 gram portions of permutit at the rate of one to two drops per second. The alcohol filtrate then contained 0.41 grams of solids and less than one milligram of adrenalin. Following concentration to 100 cubic centimeters, the filtration was repeated using two to 15 gram portions of permutit. This filtrate contained 0.4 grams of solids and 0.05 milligrams of adrenalin. The alcoholic solution was then diluted to 100 cubic centimeters and 20 cubic centimeters of distilled water was added. Concentrations of the extract depends on that desired by the producer. The alcohol was then removed by distillation and the extract again diluted to 100 cubic centimeters with distilled water. A milky suspension was obtained, but it was clarified by the Seitz filter. A clear, yellow fluid resulted. The solid content of this specimen was 0.29 grams of solids and 0.05 milligram of adrenalin. The pH of this solution was 5.65. By the addition of a 0.8 percent sodium chloride, the extract was made isotonic and could be used intravenously. This extract was quite stable, specimens of it had been stored for three weeks without any evidence of deterioration.

In another communication immediately following this one Pfiffner and Swingle report their newest and most successful attempt at preparation of a pure adrenal cortical extract (66)(71). This is their last report on the preparation, and the method is still being used. In this extract, the adrenalin has been reduced to one part in 4 million, a point far below reaction from intravenous or intraperitoneal injection. This method consists of distributing an active fraction of the cortical extract between an aqueous alkali and an immiscible solvent such as benzene or ether. The adrenalin passes into the solution of alkali while the cortical material goes to the immiscible sol-
vent phase. By this method, a highly potent extract is derived with a marked decrease in adrenalin content. The method, as described by a typical experiment, consists of preparing a 70 percent alcoholic solution, as in the two foregoing methods, from three kilograms of cortex. The solvents are removed by distillation in vacuo at 45 to 50 degrees and toward the end 30 to 50 cubic centimeters of absolute alcohol is added to facilitate the removal of water. The residue is the transferred to a separatory funnel and 100 cubic centimeters of ether added and it is washed with 50 cubic centimeter portions of 0.1 normal sodium hydroxide and then with three 50 cubic centimeter washings of distilled water. The alkali and water washings are, in turn, washed with 100 cubic centimeter portions of ether. The ether solutions and ether washings are then combined and the ether removed by distillation in vacuo and the residue is taken up with 100 cubic centimeters of 95 percent alcohol.

Eighty cubic centimeters of water is added, and the alcohol is removed by distillation, the volume of the extract brought to 100 cubic centimeters by the addition of water, and then the extract is clarified and sterilized by the Seitz filter.

The finished product in this example contained 0.23 grams of solids when finished, while the original contained 1.58 grams. The adrenalin content had been reduced to one part in 4 million from 27 milligrams in the original. The finished solution is a clear, pale yellow color and suitable for any hypodermic use. The solution is made isotonic by adding 0.8 percent sodium chloride solution.

Perla and Gottesman (47a) in 1931, did some work on isolating what they believed to be adrenal cortical hormone from the urine of humans. Using Hartman's (34) method, they claim to have ob-
tained from each liter liter of urine, hormone equivalent to that produced by 225 grams of fresh gland. This may either mean a good urine yield or a poor gland yield. Grollman and Firor (23a) in 1933, tried the same experiment, using a little different method. The yield here was not near as high as that of Perla and Gottesman, for they averaged hormone from one liter of urine equivalent to the yield from only one-half gram of gland tissue. The latter authors conclude that the urine, after all, is not so valuable as a source for the hormone. Perla and Gottesman claimed the hormone they obtained would greatly increase the resistance of rats to histamine poisoning, but this criterion should be questioned. Grollman and Firor showed the survival period of adrenalectomized dogs was prolonged only two to five days.
PART II

Analysis of the Adrenal Cortical Hormone.
Analysis of the Adrenal Cortical Hormone.

After Pfiffner and Swingle's last preparation of the cortical hormone (71), much interest has been aroused in its effects and the constituents. The last preparation of the hormone has been relatively easy to make and somewhat cheaper to process than the original preparations. Since the cost has been cut down, it has encouraged investigation and progress in the use of the hormone.

In 1931, Kendall (40) made a chemical study of the constituents of the adrenal gland as a whole. Upon his determinations he found the gland to contain epinephrine, a hexauronic acid and lactic acid. In his method, he took whole gland, ground it and added acetone, then cooled to zero, Centigrade. This was stirred three hours and the acetone pressed out, concentrated and made acid with sulphuric acid, to a pH of 2.0. This was then extracted constantly with ether. About 0.2 percent. of the raw material was found to be lactic acid. The solution was then treated with phosphotungstic acid, the excess being removed with zinc dust and barium acetate. The barium then removed and the solution concentrated to a small volume. The epinephrine was then precipitated with ammonia. This was done without the loss of hexauronic acid contained in the filtrate. Ammoniacal solution was then added to oxygen to free the lead acetate. The salt was decomposed with oxalic acid. The solution was then concentrated and treated with an ethyl alcohol and acetone which removed the organic salts and traces of epinephrine. The solution now concentrated and the residue dried at 40 degrees Centigrade. A small amount of methyl alcohol was
added and then set aside, and the hexauronic acid crystallized after several days.

Further studies were carried out by Swingle and Pfiffner (71) in 1931. In this paper, they reported various reactions of the hormone from fresh beef gland. With the Biuret, ninhydrin, Hopkins-Cole, Molisch, Pauly, Knoop and Liebermann-Burchhardt tests the reactions were negative. Positive reactions were obtained with the xanthoprotein, Millon's, alkaline copper and alkaline phosphotungstate tests. These latter tests show that there is no protein content in the extract nor any amino acid nitrogen present, as would be found in proteins. The positive reactions, however, show a presence of a dextrose and the protein reactions are probably due to the phenolic decomposition products of adrenalin which remains in the extract.

By experimental work in preparing the extract and various trials and errors, other properties have been determined.

The extract can be kept potent at room temperature over an indefinite period of time if it is preserved with a 0.1 per-cent. benzoic acid. The preservative actions of chloretone has been tested over a period of several weeks, but is ineffective and allows deterioration. The keeping quality of the extract in benzene has also been tested. Swingle and Pfiffner (71) have prepared the extract as far as the benzene extraction and left it. When extraction was completed, the hormone was just as potent as in fresh extract and revived cats prostrate from adrenal insufficiency. The fluid, when left stand over a period of time, assumes a light red color instead of a light yellow, the change probably being due to the oxidation products of adrenalin and adrenalin-like substances.

The hormone was also found to be destroyed by saponi-
fication. In a method that Swingle and Pfiffner used to prepare an extract for testing (71), they found the extract absolutely impotent. A 70 percent alcohol soluble fraction was prepared, as in the other methods (70) (71), and dissolved in 75 percent absolute alcohol. 25 cubic centimeters of normal sodium ethylate was added to the mixture and kept at room temperature and frequently agitated. The alcohol was removed by reduced pressure at 40 degrees Centigrade and the residue extracted with ether. This was washed three times with 50 cubic centimeters of water. The ether was removed, the residue taken up with alcohol and transferred to 105 cubic centimeters of water and run through the Seitz filter. The extract was tested on adrenalectomized animals and they all died of insufficiency within a few days.

The extract is also thermolabile, not withstanding a temperature of over 30 degrees Centigrade. In preparations of extracts of the hormone, care must be taken in the distillations so as not to exceed this temperature. In all preparations, the distillation temperatures were kept at 45 to 50 degrees.

Up to the time of a report made by Harrop, Pfiffner, Weinstein and Swingle in 1932, on the standardization of the hormone (24), the prolongation of the lifes of adrenalectomized animals and recovery from symptoms of insufficiency had been used as a criterion for the potency of the extracts and no attempt had been made to set a unit standard. To make a standard condition, it was found that there was no criterion for the degree of insufficiency so they could not depend on the return to normal for standardization. In standardizing a maintenance dose was given, using the blood urea and non-protein-nitrogen as a basis. The earliest changes noted were a rise in these values.
Adult dogs are used, weighing from six to ten kilograms. The dogs are required to be perfectly healthy and free from any infection since this causes an increase in the amount of extract needed. The adrenals are removed in two stages and the dogs are put on extract until the wounds are healed, and then the extract is withdrawn and the effect noted on the dogs. This is to assure the absence of any accessory gland tissue, or any that may have been missed during operation. The dogs are kept in separate kennels and given 0.5 cubic centimeters of extract per kilogram two times daily. When a constant level is reached and maintained by the Blood non-protein-nitrogen and urea, weight, food properly eaten and appear normal, the per kilogram dosage is reduced at seven to ten day intervals until a definite rise is noted in the blood fractions, and symptoms appear. The dog units are defined, then, "as the minimal daily kilogram dosage of cortical hormone necessary to maintain normal physiological condition in adrenalectomized dogs for a period of seven to ten days; the two criterion of normal physiological condition being maintenance of body weight and level blood urea and non-protein-nitrogen" (24). These units are known as Dog Units, D. U.

When each batch of extract is assayed, there is a chart kept of each dog, a record of its weight, the dosage given, days between reduction of doses and the levels of the blood urea nitrogen and clinical condition. Figure II is a typical chart of the assay data on a specimen of the extract.
Assay on Whole Gland Extract (Half Method)

Extract HM-2: 1 cc. = 40 gm gland; 1 cc. = 2.0 gm solids

<table>
<thead>
<tr>
<th>Net Kilos</th>
<th>c.c.</th>
<th>Daily dosage per Kg. mgm.sols gm.gland</th>
<th>Days</th>
<th>Urea N. mgm/100cc</th>
<th>Clinical condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.3</td>
<td>.2</td>
<td>.4</td>
<td>8</td>
<td>23 - 29</td>
<td>Normal</td>
</tr>
<tr>
<td>13.3</td>
<td>.1</td>
<td>.2</td>
<td>4</td>
<td>28 - 31</td>
<td>&quot;</td>
</tr>
<tr>
<td>13.8</td>
<td>.05</td>
<td>.1</td>
<td>2</td>
<td>31 - 34</td>
<td>&quot;</td>
</tr>
<tr>
<td>14.0</td>
<td>.025</td>
<td>.05</td>
<td>1</td>
<td>31 - 36</td>
<td>&quot;</td>
</tr>
<tr>
<td>13.5</td>
<td>.0125</td>
<td>.025</td>
<td>0.5</td>
<td>31 - 36</td>
<td>Variable appetite</td>
</tr>
<tr>
<td>12.9</td>
<td>.006</td>
<td>.012</td>
<td>0.24</td>
<td>35 - 90</td>
<td>Definite Insufficiency.</td>
</tr>
</tbody>
</table>

The end point consisted of a sharp rise in urea, followed shortly by anorexia, loss of weight, decreased activity, etc.

Figure II. Typical Assay Data (Pfiffner, Wars, Bott, Swingle (48))
PART III

Adrenal Insufficiency,
and the effect produced by
the Administration of Adrenal Cortical Hormone.
Adrenal Insufficiency, and the effect produced by the Administration of Adrenal Cortical Hormone.

Animals suffering from adrenal insufficiency, according to Zwerer (82), display a characteristic syndrome. Clinically, there is first a loss of appetite shown by the refusal of food, first solid, then liquid. Most of them will drink water until very severe symptoms set in, or to coma. Following or occurring simultaneously with the refusal of food, there is a progressive asthenia, beginning first in the hind legs, then progressing over the body. The animal merges to a state of depression. Later in the syndrome, the animal may lie prostrate on its side, or it may go into spasm resembling a Jacksonian march. In man, other symptoms occur, such as pain in the abdomen or legs, insomnia, mental depression, failing memory, lack of cooperation, aimless movements and pigmentation of the skin. The skin of the animal in later stages is dry and wrinkled and has lost its elasticity. The mucous membranes are dry. The respiration is rapid, and they may emit cries or moans with expiration. Among the early symptoms, there is a lowering of body temperature, especially noticeable in the extremities. There is a rise in the non-protein-nitrogen and blood urea, a drop in blood sugar, blood pressure and blood volume, an increase in the heart rate, the blood viscosity is raised, the red cell count is higher while the white cell count drops. A marked drop occurs in the energy output and metabolic processes are lowered. The urine output is much decreased and nitrogen output proportionally down.
The animals have a lowered resistance to bacterial and chemical poisons, wounds are slow to heal and there is a reduction in the rate and extent of body growth. All of the findings are progressive and become very severe, ending in death of the animal if treatment is not instituted.

The clinical symptoms in the syndrome are well agreed upon by the many authors that have reported upon it, the numbers of which are too numerous to list. The life expectancy of untreated adrenalectomized animals has been observed by many authors, also, and many experiments have been performed upon the significance of the adrenal cortex in the insufficiency syndrome.

By the work of Stewart and Rogoff (59) and Wheeler and Vincent (78) in 1917, the significance of the adrenal cortex was definitely established. Stewart and Rogoff showed the lack of value of the medulla of the adrenals by removing one whole gland in animals and sectioning all of the nerves to the gland on the other side. This stopped the outpour of adrenalin to the blood stream, and in no instance did such operations produce symptoms of insufficiency, nor shorten the life expectancy of the animals. Wheeler and Vincent's experiments consisted of removing one whole gland and half of the other one, then the medulla of the remaining gland was cauterized. The animal was observed over a period of three weeks, and in this time there was no sign of insufficiency, and by post mortem examination, there was no medullary tissue existing. The work of these two observers proves quite conclusively that the adrenal medulla plays no part in the life span of the animals and that the syndrome described by Zwemer, et al (82) is due to other than the medulla. On the other hand, it was left to be proved that the syndrome was
due to the cortex alone, or a secretion from the cortex. Zwemer, in 1926 (82), performed experiments similar to those of Houssay and Lewis in 1923 (38). Houssay and Lewis curetted the medulla from one adrenal gland and removed the other, leaving no medullary tissue. In this series, they reported several of the dogs were used for further experiments. Two of this series died, one at 217 days after operation, and the other at 232 days. In some of the dogs, they removed the remaining cortex, and in every instance, there was a rapid and progressive lapse into adrenal insufficiency and the animals did not live for more than 24 to 26 hours.

In Zwemer's experiments (82) with cats, one series was watched by the weight and survival period. With seven to eleven days elapsing between the removal of the first and second adrenals, the female cats were found to live only 47 to 111 hours after the second operation. The weight loss was marked during this period, ranging from 50 to 190 grams. In the male cats, seven to twenty-five days elapsed between operations, and they lived only 26 to 70 hours after the second operation. The weight loss was a little more marked, ranging from 15 to 390 grams.

Before the advent of the cortical hormone, Marine and Bauman (42) in 1926, reported a series of experiments on the prolongation of the life of adrenalectomized cats. They removed both adrenals of the animals at one operation, and the survival of untreated cats averaged 5.3 days. These animals were used for controls in their experiments. They tried the administration of a number of solutions, working on the theory that the loss of water by diuresis was the responsible factor in shortening life, and that this could be compensated by additional intake. Figure III shows the results.
<table>
<thead>
<tr>
<th>Solutions Injected</th>
<th>Number of Animals</th>
<th>Period of Survival - days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Maximum</td>
</tr>
<tr>
<td>Controls</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Thyroidectomized</td>
<td>3</td>
<td>6.1</td>
</tr>
<tr>
<td>Cortical Extracts</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>0.9% NaCl Solution</td>
<td>16</td>
<td>30.8</td>
</tr>
<tr>
<td>0.5% NaCl Solution</td>
<td>4</td>
<td>7.5</td>
</tr>
<tr>
<td>Ringer's Solution</td>
<td>25</td>
<td>34.2</td>
</tr>
<tr>
<td>Sodium glycerol phosphate</td>
<td>5</td>
<td>11.3</td>
</tr>
<tr>
<td>Sodium acetate</td>
<td>8</td>
<td>20.1</td>
</tr>
<tr>
<td>Glucose</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Glycerol</td>
<td>4</td>
<td>12.5</td>
</tr>
</tbody>
</table>

Figure III. The life duration of cats treated with solutions containing Sodium Salts, Glucose, Glycerol. (Marine and Bauman, (45))
in average survival days of the use of different solutions. It will be noted, that by the use of an isotonic salt solutions, the life span was increased almost three-fold, and the use of Ringer's solution gave almost equal increase, some individual animals surviving even longer. The use of a hypertonic solution, however, tends to cut down the life span, and lending some support to Marine and Bauman's theory of diuresis.

Hartman, et al (33), in his experiments with cats, places the life span after adrenalectomy at an average of six days, providing no accessory tissue remains in the animals body. Rats when used for such experiments, are not dependable, for a good number of them have accessory glands, and rabbits are notoriously supplied with accessories and cannot be used, for after the adrenals are completely removed, they will not develop symptoms of insufficiency.

Attempts were also made at the prolongation of the life span by thyroidectomy, which increased it to a slight extent. Zwemer, (81), in his experiments with adrenalectomized and thyroidectomized cats, showed that there was a marked prolongation of life. He found the life span to be increased almost four-fold. He believes the thyroid to have a dehydrating effect and increases metabolism. The removal of the gland tends to decrease the elimination of water and the symptoms of adrenal insufficiency, which he believes to resemble anhydremia, are postponed. He showed that to increase the amount of thyroid by feeding gland during the operative period, that death from adrenal insufficiency was hastened.

Not until the advent of the cortical hormone, did investigators succeed in prolonging the life of adrenalectomized animal any satisfactory time. The use of Pfiffner and Swingle's
lipoid extract (68) gave an enlengthened life span to the animals but they usually died of intercurrent infections produced by the lipoid injections. With the use of aqueous extracts, the animals can be kept alive for an indefinite length of time. (70)(71)

Weight loss in adrenalectomized animal is a constant symptom, and occurs concurrently with the progression of the disease. Swingle and Pfiffner (65), showed that with the withdrawal of extract there is a marked loss of weight. On experimentation with dogs and cats, and in assaying the hormone, the weight level is used as one criterion of the efficiency of the extract. ( Figure II) In preparing the animal for the assay, the weight is brought to a level as well as the blood urea, showing the animals to be in a perfectly normal condition. Upon reduction of the extract it will be noticed by the chart that weight loss was apparent before the marked rise in blood urea. Hartman (28)(33), in his article on the adrenal cortex, notes a marked loss of weight which he attributes to the gland cortex, for upon administration of sufficient amount of extract, the body weight can be maintained, and in excessive doses, animal can be made to gain weight. Several authors make note of the weight loss among the earlier symptoms of the syndrome, and note that the weight level parallels the symptoms. If an animal is allowed to slowly approach the prostration stage, the weight loss is among the most conspicuous symptoms. In removal of one adrenal gland, however, there is only a very slight loss of weight. (59)(78) The decline is very slowly progressive, and upon removal of the second cortex, producing complete insufficiency, there is a rapid decline in weight. This weight loss, however, is quickly and completely arrested upon the administration of the cortical hormone in
any of its forms (69)(70)(71), and a gain in weight could be produced. Cats have been kept alive for long periods of time and no weight loss has been noted as long as hormone is supplied in sufficient amounts.

The fall in blood pressure is one of the prominent symptoms of adrenal insufficiency, as shown by Rogoff and Dominguez (50) in their experiments with adrenalectomized dogs. Their experiment consisted of an observation of pressure before, during and after removal of the adrenals. The pressures were taken by means of a carotid loop, so that repeated readings could be taken. The pressures were read daily. During the period of good health of the dogs, no change was noticed in the pressure readings, but as symptoms of insufficiency became prominent, the pressure showed a progressive drop and within a few days of the onset of terminal symptoms and death, the pressure became very low. In Hartman, Aaron and Culp's (27) report of a case of Addison's disease, the blood pressure reading upon admittance to the hospital, while the patient was in shock, was systolic 50, diastolic 20. Upon administration of fluids, the pressure was slightly raised to systolic 58, diastolic 30, but upon the administration of cortical extract, the pressure rose as high as systolic 100. With this there was also an alleviation of symptoms.

In the recent writings of Swingle, et al (72), a report is made on the study of blood pressure, and the advancement of a new theory. For the pressure readings, the interarterial method of Domeshek and Loman was used that they might make repeated readings with acute accuracy. Table trained animals were used and the pressure taken direct from the femoral artery. This eliminated the possibility of any excitement from the operation and from trauma. Upon in-
jection of the cortical hormone, they found that there was no direct effect upon the blood pressure. As much as 30 to 40 cubic centimeters was injected at one time in normal and adrenalectomized animals without effect.

The resting arterial pressure in adrenalectomized dogs is perfectly normal as long as they are kept on maintenance doses. The average was 110 to 115 millimeters of mercury. However, upon the withdrawal of the maintenance dose of extract, the pressure dropped day by day until the death level was reached. The symptoms of insufficiency parallel the decline in blood pressure, and the latter is often among the early symptoms, for the pressure may drop to 60 to 70 millimeters of mercury systolic, before the appetite is lost. The heart rate seems to be increased as the blood pressure drops, the figures appearing in almost inverse ratio. The effect of the hormone on the blood pressure is not instant, nor direct, for the pressure is the result of increasing the blood volume or the volume of the blood plasma.

Swingle, et al (72), in their recent paper show that as high as 40 to 50 percent of the plasma volume may be lost, or even more in some cases. By the use of the "vital red" method or by the "washout method" of volume determination they show that the volume is lost within one to three days after the withdrawal of the extract, and before most of the symptoms have set in. There is a concomitant increase in blood urea and non-protein-nitrogen which these authors believe is due to the decrease in blood volume and decreased flow through the kidney. This will be discussed later. (Figure IV)

In normal animals, the loss of blood volume to a marked extent may be neither fatal nor give serious symptoms for they
Figure IV. Diagram Showing comparative Blood Changes in Normal, Treated and Untreated Animals. (Swingle, Pfiffner, Wars, Bott, Parkins (72).)
have the ability to dilute the blood by the use of tissue fluids and thus maintain their volume and pressure. The outstanding feature of adrenal insufficiency is that the animals seemingly do not have the ability to dilute the blood—the fluids cannot be called from the body tissues. By experimental hemorrhages in animal suffering from insufficiency, it was found that small hemorrhages proved fatal. In normal animals, as much as 40 percent of the total blood volume could be withdrawn at one time, and within a few hours, the volume would be back to its original height due to the compensation with fluids from the tissues. Physiologically, this is thought to be due to a decreased blood pressure in the capillaries and the filtration pressure within them no longer offsets the greater osmotic pressure of the plasma colloids, as compared with the lymph, and consequently the fluid from the tissues does not pass into the blood. In insufficient animals, it is thought that the fluid can pass into the tissues but not return, for in dogs, as much as 500 cubic centimeters of a normal salt solution has been given intraperitoneally, but no fluid was taken from it, the animal going on to death. With the use of extract in sufficient doses, the fluid, however, is rapidly absorbed and the blood pressure may rise as much as 100 millimeters of mercury per hour and in two to three hours appears perfectly normal. If an animal which has not been treated for two or three days is allowed to hemorrhage slightly, the blood pressure sinks very low and remains there for hours. No dilution of the blood occurs unless extract is given and they decline further until death. Upon the administration of even small doses, dilution of the blood is prompt, and within a few hours have returned to perfectly normal health. A loss of 5 percent of the total blood volume of an untreated dog usually proves
fatal after a few hours.

Along with the decrease in blood pressure and volume, Swingle, et al (72), noted that the viscosity of the blood increases. He explains this on purely a physical basis by the fact that there is an increased number of corpuscles per unit volume which is due to a decrease in the plasma, and an increase in plasma proteins due to the hemoconcentration. It is now the opinion of Swingle that all the manifestations which occur during adrenal insufficiency are due to the resultant progressive failing in circulation. The increased pulse rate, he argues, is due to the decreased volume also, with a lessened venous return to the right heart, and an attempt is being made to compensate this loss. Hartman, (27), in observing a case of Addison's disease, noted that the pulse was increased to about 100, and when in a prostrated condition, it was very weak and much more rapid.

A drop in body temperature, or the inability to maintain the temperature is noted in animals with adrenal insufficiency. Wyman and tum Suden (79) in experimenting with rats, placed the normal temperature between 97.9° and 100° Fahrenheit, averaging 99.1°. When placed in a cold room for two hours, seven of ten animals had a fall in temperature of 0.3° to 1.4° with an average of 0.5°, and montoward symptoms appeared. Upon return to a warm room, the temperature rose again to normal. Adrenalectomized rats that were observed had an average temperature in a warm room of 98.4° Fahrenheit. When these were placed in a cold room, there was a drop of as much as 2.2°, an average of 0.62°. Upon return to a warm room, the temperature rose to the initial level except one which had the marked fall, and it was not until two hours later that it returned. In
Figure V. Temperature Record of Adrenalectomized Rats Treated with Cortical Extract. (Pfiffner and Swingle, (66).)
another rat, a drop of 6.8° was noticed in one hour in the cold, at
the end of the second hour, a 7.2° drop. The rat was very feeble
and was cold to the touch, and upon return to the warm room, the
temperature fell to 89°, and died shortly afterward. Another rat
had an initial temperature of 95°, dropped to 90.8° in the cold,
up to 92.2° when placed again in the warm room, but did not regain
its initial temperature till the next morning. After five days, the
animal died of insufficiency. Hartman (27) noted the constant sub-
normal temperature in his case of Addison's disease. He also made
some observations with rats (32), exposing them to cold. He found
a drop of 1° Centigrade in normal rats when exposed to cold, and
as much as 12° in the adrenalectomized, with many dying. In extract
treated animals, there is a drop of two or three degrees, but they
regain their normal temperature upon returning to a warm room.
Swingle and Pfiffner (66) also made note of the striking change in
rectal temperature and its course during orxostration and treatment
with their cortical extract (Figure V). They note that coincident with
the return of rectal temperature, the appetite is renewed, metabolism
raised to normal and a disappearance of muscular asthenia. After
injection of the extract, 24 to 72 hours elapse before complete
recovery occurs.

Hartman, Brownell and Crosby (26)(32) demonstrated
the drop in temperature of adrenalectomized rats exposed to cold
when treated with cortin and sodium chloride. Four rats were each
given injections of cortical extract, three of sodium chloride in
0.5 cubic centimeter doses throughout the experiment. Four normal
rats were used as controls. The results are given diagrammatically,
Figure VI. It will be noted that the sodium chloride treated animals
Figure VI. Changes of Colonic Temperatures of Rats Exposed to Cold. (Hartman, Brownell and Crosby, (32).)
had a marked drop in temperature while those treated with cortical extract remained nearly normal. All of the sodium chloride treated rats had died by the end of the experiment, and a second series was run, with similar results.

Hartman, et al (32) demonstrated a marked drop in basal metabolism, being as much as 20 percent, which occurs along with the drop in body temperature. The rate stays at that level in most cases until just before death, when a further fall is noted (35). They computed the change in metabolism, using Meek's formula of the surface area. The animal had been deprived of food for seventeen hours, and the computations were made at room temperature (28 degrees Centigrade). Observations were made on extract treated rats and sodium chloride treated rats. Figure VII shows the amount of heat produced by the animals under each treatment. There is a decrease of 12 to 24 percent, in metabolism in the sodium chloride treated rats, while the extract treated show only a very slight decrease, in some an increase.

Webster, Swingle and Pfiffner (77) in an attempt to determine the effect of the cortical hormone on respiratory metabolism made a similar report as those above. He noted also, that the extract had no effect on normal animals. They brought up the question as to whether the thyroid played any part when the hormone was injected (77). Using cats, they did a thyroidectomy, and after two to three weeks, the metabolism had fallen 20 to 30 percent, and they showed symptoms of myxodema. Then they did a double adrenalectomy and noted the respiratory exchange daily. Here they noted a further fall in metabolism which corresponded with the development of symptoms of adrenal insufficiency. When severe, extract was given and
<table>
<thead>
<tr>
<th>NaCl rats</th>
<th>Before Adrenalectomy Cal./sq.M/hr.</th>
<th>Determinations</th>
<th>After Adrenalectomy Cal./sq.M/hr.</th>
<th>Determinations</th>
<th>Percent. average</th>
</tr>
</thead>
<tbody>
<tr>
<td>227</td>
<td>37.07</td>
<td>7</td>
<td>27.77</td>
<td>3</td>
<td>-24</td>
</tr>
<tr>
<td>229</td>
<td>36.43</td>
<td>4</td>
<td>30.52</td>
<td>3</td>
<td>-16</td>
</tr>
<tr>
<td>233</td>
<td>32.39</td>
<td>5</td>
<td>27.88</td>
<td>3</td>
<td>-12</td>
</tr>
<tr>
<td>Cortin rats</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>226</td>
<td>36.01</td>
<td>4</td>
<td>38.76</td>
<td>4</td>
<td>+ 7.6</td>
</tr>
<tr>
<td>231</td>
<td>33.31</td>
<td>5</td>
<td>32.63</td>
<td>3</td>
<td>- 2</td>
</tr>
<tr>
<td>232</td>
<td>34.63</td>
<td>5</td>
<td>36.61</td>
<td>3</td>
<td>- 5.8</td>
</tr>
</tbody>
</table>

Figure VII. Metabolism of Sodium Chloride and Cortin Treated Rats (Adrenalectomized). (Hartman, Brownell and Crosby, (32).)
the metabolism promptly rose to above normal, thus showing the respiratory changes are independent of thyroid. They also could produce a rise in metabolism above normal in cats from which only the thyroids had been removed. They believe the hormone has a direct effect on the oxidation-reduction processes of the tissues themselves. (77)

Hartman, Bowen and others (28) showed that the experimental animals had lost resistance to cold, and the metabolic rate had been lowered by 10 to 25 percent. He also showed that the body temperature dropped when the animals were exposed to cold and that some of them died. Hartman, Brownell and Lockwood (35) in 1932 collaborated the findings in earlier investigations, and they also state that cold accelerates the symptoms of insufficiency due probably to the inability to produce heat. Cortin treated animals keep pace well with the normal. It was first thought that the lowered metabolism was due to a decrease in blood sugar, but investigations show a heightened sugar when the temperature is reduced. Failure to produce heat may be explained by the lessened muscular activity due to the asthenia.

Hartman et al (35), also show that they have a lowered resistance to high temperatures. When they were subjected to a hot room for a short time, the adrenalectomized animal became restless, then shortly became quiet and slept. If left there for a longer time, they became prostrate and died. Normal control animals stirred about some, but showed no symptoms of prostration. If the adrenalectomized animal are treated with the cortical hormone, their reaction much resembles that of normal animals. The loss of body heat in adrenalectomized animals is apparently hindered and Hartman explains it on the basis of a reduction in the shift of body fluids from the body reservoirs. The water content of the skin and liver
is reduced in the untreated animals and in the extract treated, the
content of these organs is raised considerably, though not up to
normal.

Asthenia or fatigue is also one of the first symptoms
of adrenal insufficiency. Hartman, et al, (28), in a case report,
reports asthenia as one of the admitting symptoms in Addison's disease.
The patient seemed sluggish to work proposed, and when attempted
operations, tired easily and quickly. By the use of an ergometer,
an instrument for measuring the dynamic force of muscular contraction,
Hartman demonstrates only a slight loss in the contracting force, but
an early fatigue.

Hartman, et al, (35), in 1932 did some work to deter-
mine where, along the muscle-reflex arc, that early fatigue occurred.
He used rats in the experiment, one group of adrenalectomized and
untreated, and another group which was treated with the cortical
hormone. A week after adrenalectomy, the spinal cord was severed
below the level of the diaphragm, the tendon of the gastrocnemius
was cut and attached to a scale pan, and the sciatic nerve exposed
on both sides. The electrodes were arranged for direct muscle stim-
ulation; for stimulation through the nerve of the same side; and for
stimulation from the opposite nerve which was cut peripherally. A
secondary make and break coil of the inductorium was used and ad-
justed to break three times a second. The stimulus was supra-max-
imal. The stimulation was begun through the opposite nerve; when it
was fatigued, the nerve on the same side was used; upon its fatigue,
direct muscle stimulation started. By observation of the chart,
(Figure VIII) it will be seen that cortin treated animals have a
much longer fatigue period than those that were untreated. The
Figure VIII. Average Time before Complete Fatigue. Average of Sixteen Cortin Treated Rats, and Eleven Untreated Rats. (Hartman, Brownell and Lockwood, (35).)
fatigue of the muscle which occurs is of significance in the explanation of asthenia from insufficiency, for it shows that its endurance is not much over that of the nerve stimulation.

Britton and Silvette (8) report that by the use of adrenal cortical hormone in normal dogs that they can be made to do two or three times the normal amount of work. Their paper compares with that produced by Eagle, Britton and Kline (17), where they try the effect of cortin on normal dogs. They used dogs on a treadmill and worked them till they were weary or exhausted. The end point was the animal refusing to run or its lying down on the belt. After a constant energy output was established, the experiment was started, injecting the animal intraperitoneally. Immediately after the injection of the extract, the dogs were put on the mill, but no effect was noted until after four to six hours. It was found in one dog, that the output was normally 12,000 kilogram-meters, and after the injection of the extract, the energy output had been increased to 26,200 kilogram-meters, and good deal over double the original output. Upon repeated trials on the same animal, the output was found to be increased for almost two weeks after the injection, the gradually dropped down to normal. The act was carried out for almost a period of five months.

Body growth is also influenced by the administration of the cortical hormone, depending a great deal on the amount of hormone administered. In adrenalectomized animals, one of the remarkable symptoms is the rapid loss of weight which is constant unless doses of cortin are administered, and then a rapid gain of weight may be seen. (Hartman, 25). In operated animals there is a loss of appetite which is possibly responsible for the weight loss, but if treated
the appetite is often ravenous, and they eat more, in many instances, than normal animals. Hartman, et al (35), say the hormone is essential for the body growth. Castaldi (9) in 1926 reported in a foreign paper, that the cortex of the adrenal and not the medulla promotes body growth by a morphogenetic hormone produced in its cells. He states that the effect is less than that produced by the thyroid or hypophysis and possibly even less than the thymus. This conclusion was reached after many biometric, clinical and laboratory experiments. All experimental works by authors, after the isolation of the cortical hormone, shows that there is an increase in body weight following administration of adequate doses. The growth follows closely that of normal animals. (28)

The healing of wounds is closely related to body growth and the recovery from insufficiency. Hartman, Brownell and Lockwood (35) observed that the healing of wounds after removal of the adrenals was greatly enhanced by the administration of the hormone immediately. The animal requires more hormone when injury is inflicted, for if an animal is put on a maintenance dosage and then a operation is performed, healing will take place slowly if at all unless the dosage is advanced. (28) Until the hormone was isolated, it was felt that only one gland could be removed at a time due to the amount of shock, and the animal would lapse into coma, but now both glands can be safely removed at once, with the immediate administration of cortin.
Much work has been done on the blood changes in adrenalectomized animals, and the effect of the cortical hormone on them. The earliest and most significant of the changes is the shift of the blood urea and the non-protein-nitrogen. These two factors are the first disturbed, and are used in the biological assay of the hormone (24)(48).

Swingle (62), in 1926, noted a sharp rise in the non-protein-nitrogen in the blood of adrenalectomized animals, and said it may reach great heights. Even in unilateral adrenalectomized animals, the non-protein-nitrogen has reached as high as 42 to 47 milligrams percent and in bilaterally operated animals, with serious symptoms, reached 91 milligrams percent. The level is highest when the animal is approaching coma. The change from normal is early and may be apparent within the first twenty-four hours. After the initial rise, the height gradually progresses until the pre-coma stage, when the rise is sharp. The highest rise noticed by Swingle was 170 milligrams percent. Zwemer (80) also reports a similar rise, going from 43 to 88 milligrams percent after bilateral adrenalectomy. He was surprised to find that the removal of one gland gave a shift toward the above figures, but the outward appearance of the animals remained the same. Hartman, Brownell and Lockwood (35) showed that the non-protein-nitrogen was raised in the blood stream, but was lowered in the urine. The administration of cortin counteracts the rise in non-protein-nitrogen, bringing it down to almost normal limits. His explanation of this situation is the increased water intake and urinary output, thus helping to establish the nitrogen balance by
increasing circulation in the kidney. Late in the stages of insufficiency, the water intake is much reduced, and the body may become quite dehydrated and circulation very sluggish (72). Britton, Flippip, and Silvette (5) also showed that by the administration of the hormone the non-protein-nitrogen level could be brought back to normal; in one experiment, it dropped from 50 to 24 milligrams percent very soon after administration.

Blood urea also shows a marked increase. Swingle (62) established normal cats at 19 to 24 milligram percent and he observed in operated animals, a rise ranging from 40 to 122 milligrams percent. Hartman, et al, (27) noted similar changes in a man suffering from Addison's disease. He noted that the urea was as high as 130 milligrams percent during the first three days in the hospital, but that it fell rapidly upon the administration of cortin and the disappearance of symptoms. The patient has several relapses and with each, had a rise in blood urea, but upon revival from the relapse, the urea would not be lowered immediately with the amelioration of symptoms.

Hartman (25) in his experiments with animals and their reactions to cortical hormone, noted also that there was marked drop in the blood urea after the administration (Figure IX), but if the urea is already low, doses of the hormone do not effect it. Swingle (62), in another article, noted that the urea is usually higher in treated animals than in the normal, though not remarkable. In animals treated with concentrated and with dilute extracts, in spite of the larger food consumption in the former, the blood urea is no higher. The extract when given by mouth, seems to have no effect on the urea. Swingle, et al (72) believe the blood pressure is probably respons-
<table>
<thead>
<tr>
<th>Cat</th>
<th>Days after Operation</th>
<th>Time</th>
<th>Injection</th>
<th>Blood Urea Nitrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>9:00 a.m.</td>
<td>Cortin</td>
<td>68.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12:00 m.</td>
<td></td>
<td>54.0</td>
</tr>
<tr>
<td>18</td>
<td></td>
<td>9:00 a.m.</td>
<td>Cortin</td>
<td>84.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12:00 m.</td>
<td></td>
<td>62.0</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>10:00 a.m.</td>
<td></td>
<td>93.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12:30 p.m.</td>
<td></td>
<td>92.3</td>
</tr>
<tr>
<td>52</td>
<td></td>
<td>9:30 a.m.</td>
<td>Cortin</td>
<td>80.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12:24 p.m.</td>
<td></td>
<td>58.0</td>
</tr>
</tbody>
</table>

Figure IX. Blood Urea in Cortin Treated Adrenalectomized Cats. (F.A. Hartman, 25.)
ible for the rise in blood urea, and non-protein-nitrogen. These vary in almost inverse proportion. When the cortical extract is given, the blood pressure rises and the blood volume increases before the urea and non-protein-nitrogen go down. There is a lag of from 24 to 48 hours.

The protein and total nitrogen content of the blood in adrenalectomized animals also shows an increase, but this is not so marked as might be expected from the concentration of the blood plasma. In unilateral adrenalectomized animals, it has reached a figure of 1.41 percent, and bilateral, 1.49 percent.

The nitrogens of the blood can be divided into many factions, but in adrenal insufficiency, it suffices to say that all of the nitrogens are increased. The blood urea parallels the non-protein-nitrogen for it forms about 45 to 60 percent of the non-protein-nitrogen.

The calcium content of the blood seems to make no significant change; a slight rise in calcium occurs and a slight fall in the sodium. These seem not to vary between unilateral and bilateral adrenalectomy. The blood phosphorus, on the other hand, gives as striking and constant rise, ranging from 15 to 16.5 milligrams percent, in the precoma and coma stage, while in the unilaterally operated animals, it ranges from 4.5 to 9.8 milligrams percent. The rise in phosphorus occurs along with the increase in severity of the symptoms (62). The rise indicates the approach of a coma or convulsion and it was thought it might be used as a prognostic sign. The rise in phosphorus is not to be considered as a terminal event, even though the most marked rise does occur then. The concentration of the blood cannot be held responsible for this rise,
for by dilution with Ringer's solution, no change occurs in the phosphorus value.

Putschkow and Krassnow (49) claim that the increase in amino-acid and amino-nitrogen in the blood and urine indicate a cessation of liver function. The isolated liver of adrenalectomized cats acts on ammonium salts and biogenous amines more feebly than normal. The use of the extract, however, restores this barrier function of the liver to its normal capacity.

Only slight mention is made of the blood chlorides. They were found to decrease from 625 to 575 milligrams percent. in a series of experiments run by Zwemer in 1931 (80). He also made observations on the carbon-dioxide combining power of the blood and found that a similar drop occurred here. The values found in his series averaged a drop from 37 to 23 volumes-percent. The hormone, however, restores these to nearly normal.

The blood sugar level in insufficiency always shows a marked drop. In bilaterally adrenalectomized cats, blood sugar drops from its normal, 105 to 110 milligrams percent. to 40 to 60 milligrams percent. at the time of death. In cats, this occurs in about sixty hours. The drop is first noticed in fifteen to twenty hours after the operation and assumes a progressive course. (62). Weakness and cerebellar symptoms are coincident with the drop in blood sugar, these beginning to show when the sugar reaches 75 to 80 milligrams percent. and coma sets in when it reaches 40 to 55 milligrams percent. The hypoglycemia, however, is not the cause of death, for glucose has been given intravenously, and the animals have gone on to death with a high blood sugar, though the life span may be prolonged. Cats have been injected with insulin and passed
into coma and convulsions when the blood sugar has reached 40 to 45 milligrams percent., the same as in bilaterally adrenalectomized animals. Cori and Cori (14) claimed that the lowered blood sugar is due to a lowered glycogen reserve in the liver. Such rats formed glycogen from glucose at normal rate. They suggested that there is a disturbance in formation of glucose from protein due to a lack of adrenin or cortin. Experiments show that the inhibition of the glycogen formation in the liver in adrenalectomized rats which follows the injection of insulin is not due to adrenin. This experiment was carried out before the isolation of the cortical hormone. In the case of Addison's disease reported by Hartman (27) the blood sugar was down to 82 to 86 milligrams percent. even during the administration of glucose, which is normal persons, raises the level. The sugar was not particularly low, but there was considerable fluxuation in the level.

The first observation made of the effect of the cortical hormone was by Britton and Silvette (8). When they used the extract, they noticed a rapid change in the animals behavior, approaching the normal, and the life expectancy was much prolonged, the animals gained weight, their appetite was much improved, and the noticed that the blood sugar was again brought back to the normal level, and remained there as long as the animal was kept on sufficient hormone. (35) Britton and Silvette (7) did a good deal of work on the carbohydrate metabolism in rats. He used normal animals weighing 30 to 60 grams, which were all fed alike. The test was made after a fasting. A cortical extract was used in which one cubic centimeter equaled the yield from 40 grams of cortex and the adrenalin content was one in two million parts. For controls, one series was injected with
<table>
<thead>
<tr>
<th>Materials Injected</th>
<th>Number of Animals</th>
<th>Muscle Glycogen mgm. %</th>
<th>Liver Glycogen mgm. %</th>
<th>Blood Sugar mgm. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extract - 6 doses</td>
<td>10</td>
<td>0.463</td>
<td>0.78</td>
<td>132</td>
</tr>
<tr>
<td>Extract - Large D.</td>
<td>23</td>
<td>0.523</td>
<td>1.12</td>
<td>317 (high)</td>
</tr>
<tr>
<td>Extract - Av. of all</td>
<td>32</td>
<td>0.489</td>
<td>0.95</td>
<td>144</td>
</tr>
<tr>
<td>Adrenalin 1:2000000</td>
<td>14</td>
<td>0.246</td>
<td>0.31</td>
<td>110</td>
</tr>
<tr>
<td>Saline - normal</td>
<td>10</td>
<td>0.287</td>
<td>0.32</td>
<td>87</td>
</tr>
<tr>
<td>None - non-fasting</td>
<td>6</td>
<td>0.466</td>
<td>1.05</td>
<td>113</td>
</tr>
</tbody>
</table>

Figure X. Average of the Tables and the Effects of Cortical Extract, Sodium Chloride and Adrenalin upon Carbohydrate Levels in Normal Rats. (Britton and Silvette, (7).)
adrenalin equivalent to that in the extract, and another series injected with normal salt solution. By such experiments, they showed that the blood glucose and liver and muscle glycogen were higher in the extract treated animals than the others. (Figure X.) Larger doses of the extract gave even higher values of glycogen and sugar levels, which often gradually increased for a period of three hours. Considerable variation of dosages showed that the blood sugar raise paralleled the dosage, but the glycogen levels did not follow in this manner. Adrenalin also gave slightly higher levels in blood sugar, but the glycogen levels were lower, even more so than with salt solution. Britton and Silvette believe this blood sugar raise to be emphatic indication of the potency of the extract, and that the extract is of far reaching importance in the control of carbohydrate metabolism. In insufficiency, they believed the derangement of the sugar and glycogen metabolism was sufficient to produce death. Figure XI shows the level of the carbohydrates through a typical insufficiency period, with the revival by use of the cortical extract. In the adrenalectomy of a totally diabetic animal produced by pancreatectomy, there was still a fall in the blood sugar and also in the glycogen. This relation between the adrenals and the pancreas is subject to further study. In the diabetic animals the blood sugar ran from 200 to 300 milligrams percent, while the liver and muscle glycogen ran 400 and 450 milligrams per 100 grams of gland tissue respectively. The adrenalectomized animals show are unable to store sufficient glycogen in the liver, averaging about one-tenth the normal amount.

Medvedeva (43) demonstrated that the suprarenal cortex contained a substance which when injected subcutaneously, pro-
<table>
<thead>
<tr>
<th>Condition of cat and time</th>
<th>Muscle Glycogen</th>
<th>Liver Glycogen</th>
<th>Blood Sugar</th>
<th>Lactic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>48 hours after Operation, Weak and Comatose Condition</td>
<td>0.315</td>
<td>0.179</td>
<td>55</td>
<td>28</td>
</tr>
<tr>
<td>2 to 8 days after Operation, Weak, Extremis, Convulsions</td>
<td>0.231</td>
<td>0.061</td>
<td>46</td>
<td>35</td>
</tr>
<tr>
<td>Partially Restored by Extract</td>
<td>0.600</td>
<td>0.489</td>
<td>109</td>
<td>31</td>
</tr>
<tr>
<td>Completely Restored with Extract--Attempted to take Food.</td>
<td>0.401</td>
<td>0.59</td>
<td>101</td>
<td>26</td>
</tr>
</tbody>
</table>

Figure XI. Glycogen and Blood sugar Levels during Insufficiency and Recovery with the Cortical Extract. (Britton and Silvette, (6).)
duced as hypoglycemic effect two to two and one-half after injection. Some sugar levels dropped till only traces were left. He believed this to be an entirely separate hormone which he calls "Corticaline." This effect did not depend on insulin, for the effect was the same in diabetic dogs. This demonstration is entirely contrary to those of other authors on the extracts from the sucraremal cortex, and would bear further investigation, but no more work could be found.

Silvette (56) experimented on the effect of cortin on glucose in the presence of blood in the test tube. He found that it greatly increases glycolysis if not in too great concentrations. He found that for a given amount of blood, there is an optimal content of extract necessary to give the maximal rate of glycolysis. Adrenalin had no effect on glycolysis, nor did boiled extract.

The blood cellular changes in adrenal insufficiency are quite marked. Corey and Britton (12) reported experiments with cats in 1932 and noted that there was almost a sixty percent rise in the erythrocyte count, ranging from a normal average of 9,300,000 cells per cubic millimeter to 15,500,000 cells in insufficiency. They believe that this rise in cell count is due to the concentration of the blood from the loss of fluids. This later was affirmed by Swingle, et al (72). Leucocytic changes are just the opposite, giving a marked drop in count (Figure XII). In cats, the normal value averages about 12,000. Within a few days after removal of the adrenals, there was a drop to an average of 7,000 cells per cubic millimeter. One animal dropped to 2,800. An interesting change is noted in the differential count quite early. There is a marked drop in the percentage of the neutrophiles and a corresponding increase in
### InjBction

<table>
<thead>
<tr>
<th>Injection</th>
<th>Erythrocye Count - millions</th>
<th>Difference millions</th>
<th>Percent Differ.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>In insufficiency</td>
<td>After Treat.</td>
</tr>
<tr>
<td>Adrenal Extract</td>
<td>11.2</td>
<td>18.6</td>
<td>13.9</td>
</tr>
<tr>
<td></td>
<td>6.9</td>
<td>17.6</td>
<td>13.3</td>
</tr>
<tr>
<td>Adrenalin</td>
<td>11.9</td>
<td>14.1</td>
<td>14.2</td>
</tr>
<tr>
<td></td>
<td>6.9</td>
<td>17.3</td>
<td>17.1</td>
</tr>
</tbody>
</table>

#### Leucocyte Count – thousands

<table>
<thead>
<tr>
<th>Injection</th>
<th>Leucocyte Count</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal Extract</td>
<td>7.6 11.2</td>
<td>+ 3.6</td>
</tr>
<tr>
<td></td>
<td>10.4 16.8</td>
<td>+ 6.0</td>
</tr>
<tr>
<td></td>
<td>11.2 13.0</td>
<td>+6,500</td>
</tr>
<tr>
<td></td>
<td>8.8 12.4</td>
<td>+ 3.6</td>
</tr>
<tr>
<td></td>
<td>12.4 16.6</td>
<td>+ 6.2</td>
</tr>
</tbody>
</table>

### Differential White Count – percent.

<table>
<thead>
<tr>
<th>Normal Leucocyte</th>
<th>Normal Lymphocyte</th>
<th>Before Extract</th>
<th>After Extract</th>
</tr>
</thead>
<tbody>
<tr>
<td>53</td>
<td>43</td>
<td>3</td>
<td>24</td>
</tr>
<tr>
<td>66</td>
<td>28</td>
<td>44</td>
<td>73</td>
</tr>
<tr>
<td>52</td>
<td>42</td>
<td>26</td>
<td>48</td>
</tr>
<tr>
<td>80</td>
<td>14</td>
<td>63</td>
<td>91</td>
</tr>
</tbody>
</table>

**Figure XII. Blood Cellular Changes in Insufficiency and Cortical Hormone Treatment. (Corey and Britton, (12).)**
the percentage of the lymphocytes. The granular cells may reach as low as three percent, when external symptoms of insufficiency are
marked. (Figure XII) These changes become progressively worse unless the cortical hormone is administered, then within a few hours the red and white cell count is back to the normal level, but the differential count is lagging in its return. The white cell count may exceed normal in some animals for a few days, but readily returns. Adrenalin has been tried on such cases, but was found to give only a slight shift toward normal and the action is fleeting.

Blood sedimentation time had been studied in 1927 by Borcilla and Maya (4) in a series of twenty-four cases of Addison's disease, and they found it had been accelerated to a marked degree. It is said to appear early and is a constant finding. They believe it is of prognostic value, the more rapid the sedimentation time, the graver the disease. It has been noted, since the use of cortin in Addison's disease, that the sedimentation time lengthens to nearly its normal value.

In adrenal insufficiency, there is a marked suppression of urine output which develops as the seriousness of the general symptoms increase. For the first few days, the output may be normal or only slightly decreased, but become progressively less until just before death, there is very little or no urine. An analysis shows a small amount of albumin. Swingle (62), on the strength of this and the phosphorus and nitrogen retention, studied the kidneys for degenerative changes, but found only a few hemorrhagic areas. He believed the kidney was involved in the syndrome causing death, based on the acid-base equilibrium, which will be
discussed later. Hartman, et al (35), noted that the non-protein-nitrogen of the urine was lowered in both intentional adrenal insufficiency and in Addison's disease. By the use of cortin, the non-protein-nitrogen ratio of the blood and urine was changed and there was a rise in urine output, corresponding to the water intake. They noted that late in the insufficiency syndrome, the water intake is much reduced and body may become dehydrated. The hormone reestablished the water balance (35)(72)(62). Swingle (63) attempted to demonstrate a lesion in the kidney, but found none, and decided that any renal lesion that occurred, if any, was a functional one.

Silvette and Britton (57) showed lately that the administration of cortin was soon followed by urination. They demonstrated the kidney function in adrenalectomized rats by administering 20 cubic centimeters per 100 grams body weight in twenty-four hours and noting the effects in treated and untreated animals. He found that the untreated (sodium chloride injections) rats excreted more chlorides and less water, and were unable to excrete water that was injected intraperitoneally. (also 72). Animals which were given urea, sodium chloride, water and glucose, plus one dose of the cortical hormone showed a profuse outpouring of urine rich in chlorides and urea. Normal and extract treated adrenalectomized react similarly. It was found that small doses of urea were toxic to adrenalectomized animals, 0.1 milligram in twenty-four hours giving a reaction, while normal animals could tolerate as much as 0.8 milligrams, and cortin treated animals were given as high as 1.3 milligrams without a reaction.

The phenosulphophthalien test in adrenalectomized and normal rats were comparatively equal. The use of cortin did not
increase the output of dye, but did increase the fluid output (57).

As seen by Swingle's (72) experimentations on the distribution of body fluids, there is a marked disturbance of water balance. Britton and Silvette (57) also claim that with water being drawn from the blood stream into the tissues, the osmotic pressure would rise. The retention would appear to be brought about by means of diminution of the blood chlorides which are found to be excreted in large amounts in the urine. The transference of water from the blood to the tissues may be the result of increased permeability of the blood vessel walls permitting plasma to escape. If this happens then the kidney, in insufficiency, would function with very delicate efficiency, holding back water and eliminating ions which disturb osmotic relationships. Swingle (62) suggested that the adrenal gland gave off a hormone necessary for maintenance of normal kidney function before he isolated the hormone of the cortex.

He (Swingle) believed that the shift in the acid-base equilibrium was due to an uncompensated, non-volatile acidosis from an increase in phosphorus and organic acids and was the cause of death in adrenal insufficiency. Data indicated that one cause was the retention of acid end products of katabolism and the kidney failed to properly perform acid eliminating processes in relation to body neutrality regulation. For some time, the respiratory mechanism is sufficient to care for the acidosis by throwing off volatile acid, but finally the respiration is inadequate and the pH falls, acidosis supervening. Respiration fails and death is from acidosis and respiratory failure. A year later (1928), Swingle (61) did a further determination on blood constituents (Figure XIII) and concluded that there was a definite fall in body pH, and acidosis was due mainly to increase in phosphorus and organic acids.
<table>
<thead>
<tr>
<th>Determination</th>
<th>Unilateral Adrenalectomy</th>
<th>Bilateral Adrenalectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Protein</td>
<td>5.89-7.78 %</td>
<td>6.11-8.42 %</td>
</tr>
<tr>
<td>Serum Protein</td>
<td>10.1-13.6 mm.</td>
<td>10.2-13.2 mm.</td>
</tr>
<tr>
<td>pH</td>
<td>7.26 - 7.48</td>
<td>7.11 - 7.39</td>
</tr>
<tr>
<td>Carbon-dioxide Tension</td>
<td>26.7-42.7 mmHg.</td>
<td>31.5-30.7 mmHg.</td>
</tr>
<tr>
<td>Serum Bicarbonate</td>
<td>15.5-12.6</td>
<td>9.7-11.7</td>
</tr>
<tr>
<td>Serum Chlorides</td>
<td>103.1-118.5 mm.</td>
<td>106.0-115.9 mm.</td>
</tr>
<tr>
<td>Serum Phosphorus</td>
<td>2.5 - 5.6</td>
<td>3.6 - 6.3</td>
</tr>
<tr>
<td>Total Acid</td>
<td>137.6-154.1 mm.</td>
<td>130.6-164.4 mm.</td>
</tr>
<tr>
<td>Total Base</td>
<td>154.4-186.14 mm.</td>
<td>141.5-164.4 mm.</td>
</tr>
<tr>
<td>Organic Acid</td>
<td>8.4 - 43.1</td>
<td>10.9 - 21.7</td>
</tr>
</tbody>
</table>

Figure XIII. Blood Determinations in Unilaterally and Bilaterally Adrenalectomized Cats. (Swingle and Eisenman, (61).) (1927)
Vincent (75) with his experiments with adrenalectomized animals noticed that when in dire extremis, respiration ceased, but the heart still beat strongly. By injection of a watery extract of the suprarenal cortex, the respiration was restored, and finally to normal. An extract from the medulla produced no such an effect, and he concluded that some substance essential for respiration, was produced by the cortex. He called this "pneumin." By ligation of the blood supply to the adrenals, he also claimed this passed by way of the lymphatics. (76) These works were done before the advent of Swingle's cortical hormone and his extensive experimentation with it.

Considerable controversy has arisen over the effect of the cortical hormone on sexual development and function. Deanesly (15) observed the growth of the cortex in rats, and noticed that in the female, about two-thirds of the cortex was occupied by a dark staining "x" zone. As the rat matures, the "x" zone begins to disappear and at about three weeks, is similar to the male adrenal cortex. The inner zone of the cortex disappears in the male, but in the female, it grows rapidly till about five weeks, when it equals about one-half the cortex. He doesn't tell at what age the "x" zone begins to break down, but in some, may remain for twelve weeks. Pregnancy, he notes, causes a rapid and complete degeneration of the "x" zone. Castration of the male causes an increase in size of the adrenal cortex, but not in the medulla. It then develops an "x" zone equal to that of the female. Muller (45) made an extract of the cortex and injected it in the female rats, and found that it inhibited sexual maturity, both on internal and extern-
al genitalia, with a non-development of ova and corpus leuteum. Asher and Klein (2) confirms these findings. On the other hand, Englehart (18), with the use of an extract he prepared, demonstrated as three-to four-fold increase in the size of the uterine mucosa and musculature. Corey and Britton (13) confirms Englehart's results with the use of Swingle's (71) aqueous cortical extract. They state that there is marked early maturation, the development of corpus leuteum and uterine hypertrophy, and the ovaries showed large follicles. An increase in the size of the pituitary also occurred. This was all evident in twenty-eight days, and from then on there were increasing signs of sexual precocity.

In the male, hypertrophy action also takes place, according to Zwemer (80), with an increase in the number and size of the interstitial cells. Asher and Klein (2), working entirely independent, report the same findings, with an increase in size of the epididymus, seminal vesicles and penis. Hartman, Brownell and Lockwood (35) report the development of sexual precocity in both sexes, but say it is more pronounced in the female. Corey and Britton (13), however, argue that there is usually no increase in the size of the testes, though he did get marked enlargement in two cases. Microscopically, he found longer tubules, compressed and packed, and spermatogenesis occurring in almost double the number of tubules. The marked enlargement of the pituitary that he finds occurring in these cases, may be due, he believes, to the enhancement by the extract, and it in turn, acts on the gonads, though, on the other hand, may be purely incidental and not effect the gonads. Gaunt and Parkins (21), in furthering the experiments on the effect of cortical hormone on the sex organs, denies any advancement in
development of the organs. They used an extract of the whole gland which is prepared commercially (Eschatin; Park, Davis and Company). They declare that in no cases did ovulation occur, corpus lutea develop nor changes occur in the uterus; they are just as emphatic about the lack of change in the male. The extract, however, was potent, for the animals were able to become pregnant, deliver and lactate normally. The author doubts the validity of the relationship between adrenals and gonads under normal conditions.

Animals suffering from adrenal insufficiency, have a marked lowering of resistance to bacterial toxins. Such animals, when exposed to toxins such as typhoid vaccine or dead staphylococcus, seldom recover. However, if given doses of extract, then exposed, as high as 70 percent, live down the toxic effects. If an animal is kept on a maintenance dosage of extract and then exposed to toxins or minor injury, a much larger dosage is necessary to keep them from succumbing. The same holds true for Addison's disease in humans, and as will be seen by the following case reports, many of the maintained cases die of intercurrent infections.

Hartman (25)(31) says the animals have a low line of recovery both for operation and infections, but when treated, have an unusually high resistance. This may be due to the restoration of the leucocyte count as well as an improvement in the general body condition.

Perla and Gottesman (47) demonstrated the lowering of resistance to a chemical poison--histamine. A young adrenalectomized rat could stand 120 to 200 milligrams of histamine per kilogram while
the adult had a minimal lethal dose of 100 to 120 milligrams per kilogram. By using one-half cubic centimeter of cortin (one cc. equals four gram cortex) twice daily, the resistance was raised to three to four minimal lethal doses. They suggested the ability of the cortical extract to protect animals against histamine as a method of assay, but it has not been developed. Coombs, et al (11), used absinthe in a similar experiment, and found that the resistance was lowered 33 to 50 percent. in adrenalectomized animals. By the use of the cortical hormone, it was again raised to normal, thus producing further evidence of the increase in resistance produced by the cortical hormone.
PART IV

Indications for the Use of
The Adrenal Cortical Hormone

and

Case Reports
Indications for the Use of
The Adrenal Cortical Hormone and Case Reports.

Addison's disease is, of course, the main disease in which the cortical hormone is used. It is the lacking element which is the base of all symptoms appearing in that disease. Up till the time of the isolation of the cortical hormone or Cortin, in 1930, the Muirhead treatment, devised by Rowntree was used for Addison's. This consisted of tolerance doses of adrenalin and quantities of dessicated adrenal cortex or whole gland given by mouth. This treatment was only partially successful, and gave relief only in the mild cases, while those suffering from a severe insufficiency, obtained only slight symptomatic relief and nothing permanently of any help, the malady often becoming progressively worse.

Since the advent of the cortical hormone, the treatment of Addison's has been revolutionized. When one has been put on maintenance doses of the extract, the symptoms disappear, they gain weight, become strong physically, and are restored to seemingly normal health. Adrenal insufficiency resembles other endocrine disorders, in that as long as they are kept supplied with the missing element, they are, to all outward appearances, normal, but as soon as the treatment is slackened, or infection intervenes or other upsets occur, they are thrown from this fine balance and again lapse into their original syndrome. Recovery with the use of the adrenal
cortical hormone has seemed to be, in most cases, almost miraculous, though it does sound expeditious, recovery has been made from coma and the patient restored to nearly good health.

The cortical hormone, when given, is usually administered perenterally. Since the aqueous extract was prepared by Swingle (71), it can be administered by any of the following routes: subcutaneously, intermuscularly, intraperitoneally or intravenously. The former three are used in the maintenance cases, where a small dose is given at measured intervals, but in a case in extremis, either coma or convulsions, the extract may be given by the intravenous route, for absorption is much more rapid, and the recovery brought about with less delay. Oral administration has been tried by a few men, but has not been found so practical, for the extract is about one-fifth as potent by mouth. Also, in the insufficiency cases, the gastrointestinal tract is very irritable, and often small doses by this route are vomited. It has been tried in milk, salmon and various other disguises. (5) The use of the extract subcutaneously is often too irritating, and the intramuscular route has been made the one of choice.

The dosage of the extract varies considerably, depending on the severity of the condition, and the potency of the extract. That being prepared now usually contains in one cubic centimeter, the yield from 30 grams of beef cortex, the whole supply from two steers. In Addison's disease, Rowntree, et al (54), have given as much as twenty cubic centimeters intravenously in one day, though in the maintenance case, the course of treatment usually consists of administering from 40 to 60 cubic centimeters over a period of four to ten days. Those patients who are seriously ill
may need continuous treatment with from three to 10 cubic centimeters daily. One patient received 500 cubic centimeters in two months. In patients who are able to maintain partially reduced or normal activity, may, with the aid of the Minnihan treatment, need only an occasional injection of the extract to combat infection, fatigue, and such symptoms of insufficiency.

The cost of the extract, though somewhat cheaper than it was at the beginning, would still be about three thousand dollars a year for the amount necessary to be effective in a case of Addison's disease. Even in glandular failure, the replacement therapy is at a minimal, the cost would amount to at least one hundred dollars a year.

Case Reports:

Case #1: A man, age 24, came in noting fatigue, gastrointestinal upsets, anorexia, nausea and vomiting, which came in spells of increasing frequency during the past six months. He came to the hospital in coma, irrational. Blood pressure, systolic 50, diastolic 20. At first, he received adrenalin without help, then cortin equivalent to 3200 grams of gland was administered. Marked help was noted in six days. When the dosage was cut below the equivalent of 1000 grams per day, he had relapses. If stopped cortin, would have a complete relapse in three days, and it would take as long to recover. The patient was kept alive for 224 days, when he developed an extensive upper respiratory infection and died. The patient showed almost complete relief from symptoms. The blood pressure went up to systolic of 85 to 100, temperature 97°, blood urea nitrogen fell from 120 milligrams percent to normal. The blood sugar reached a low point of 75 milligrams percent. Basal
metabolic rate was -7 to -15 percent. In the terminal event, the temperature went to 105°, the white blood count to 30000 with 85 percent neutrophils. The extract was increased to the limit they had on hand, but died in twenty-four hours.

Autopsy revealed an atrophy of both adrenals. Weight 3.44 grams. Old calcified tubercle of a lymph gland. Diagnosis, Addison's disease. (28)

Case #2: A man, age 24. Scarlet fever in February, 1928, ill one month. During winter, 1929 and 1930, he continued work, but lost vitality toward evenings. Had two quite severe gastric upsets.

On hospital admission, had been ill for six weeks, nausea and vomiting frequently, and could only retain liquid foods. Had a twenty percent weight loss. Had the characteristic pigmentation of face, neck, arms, exposed parts seemed strongly sunburned, in addition, black freckles over body. Brown streak on skin above spine and brown discoloration of hips and some of gums.

When first seen, in shock, the pulse was feeble, blood pressure, systolic 50, diastolic 30. He felt cold, so applied blanket and hot water bottles. Gave lots of water, 1000 cubic centimeters of isotonic sodium chloride hypodermically and a small amount of water by mouth. Six hours later, 5 percent glucose with isotonic sodium chloride, 1000 cubic centimeters. He was given four or five liters of water in the next 24 hours.

He was drowsy and dozed most of the time. Not much better in 24 hours. Blood pressure, systolic 58, diastolic 30. His pulse was weak, he was restless, throwing hands and feet about, twitched. He said he felt numb and tingled. Talked irrational.
Adrenalin was administered in one cubic centimeter doses every two hours, and stopped on the third day. 5 percent. glucose was given three times a day for seven days, and digitalis for three days. Cortical extract was not available for twenty-four hours after admission. Upon receiving it, five cubic centimeters were then given, thirty minutes later, another 10 cubic centimeters. Three and one-half hours after first injection, three to 10 cubic centimeter doses were given. Injections were made every 40 to 70 minutes. No more extract was available for four hours, then 10 cubic centimeters were given every hour until 150 cubic centimeters were given.

Three hours after starting the extract, the patient was quieter, and at nine hours, the pulse was 100, temperature 100°, and respirations, 26. He again became irrational, voided in bed. By morning, (20 hours) he slept at long intervals, but restless. During the next night, he was restless and irritable. Pulse fair, blood pressure, systolic 74, diastolic 32. He improved during the third day, dozing. Slept the third night, and brighter the fourth day. He ate his first meal and took interest in his surroundings. Appetite was good, and generally improved. No longer slept during the day, and much brighter.

The cortin was then reduced until he was receiving only 20 cubic centimeters in 24 hours, and at 11 days he began to refuse food, felt cold, and by 11 p.m. was very ill and nauseated. The cortin was stepped up, giving 10 cubic centimeters intravenously and 10 cubic centimeters every hour, for 36 hours. The dose was then cut to every two hours, but relapse occurred again, so it was stepped up again.

An attempt was made to find the minimum dosage, but
when cut down, relapse occurred, so again increased the dosage, and recovery again apparent. They tried discontinuing the extract all but one day from eight, but the old symptoms occurred, and again had to increase.

The patient was kept alive for five months with cortin, and only one more relapse occurred. (27)

Case #3: White married woman, age 37. She was first seen at Johns Hopkins Hospital February, 1930. She complained of weakness, two years duration. Gradually a loss of energy for four or five years before the onset of definite symptoms. Her systolic blood pressure was reported at 95 millimeters mercury in 1928 and then the skin began to darken. On examination in 1930, a moderate diffuse, brownish pigmentation of skin in the typical distribution with pigmented areas on the gums and buccal mucosa. The blood pressure, systolic, 98, diastolic 65. Diagnosis, Addison's disease.

Treatment with the extract of the suprarenal cortex began on July, 1930 and continued till November, 1930, with definite subjective, but not objective improvement. She was not again seen till April, 1931. During the interval, she experienced increased weakness and pigment became darker. Blood pressure was 70/50. She was again admitted to the hospital and shortly afterward passed through an acute attack of suprarenal insufficiency followed by two milder attacks in May, 1931. All successfully treated with the cortical extract and intravenous glucose. After discharge from the hospital at end of July, 1931, the patient was given injection of extract every two weeks and continued in excellent condition with the exception of a minor relapse in October, 1931. She came to the
dispensary on January 15, 1932 for biweekly injections of the extract. She was generally in good condition. The following day, she ate a heavy midday meal, followed by a gastric upset. During the night, she had shortness of breath, pain about the heart. She was drowsy the next morning and remained in bed where her husband found her dead at noon.

Autopsy was performed five hours after death, and examination of the adrenals showed the cortical cells completely lacking in all microscopic sections. (16)

Case #4: A married, white man, age 34, first seen in Johns Hopkins Hospital April, 1931. Complained of general weakness, which had developed insidiously since August, 1930. Darkening of the skin was first noticed February, 1931. On examination in April, 1931, the skin was all a pale brown color, intensified over the face, back of hands, forearms, and ventral trunk, a triangle of dark area over the lumbosacral region and the perineum was darkly pigmented. The blood pressure was 105/55. Diagnosis, Addison's disease and the patient was admitted to the hospital. Shortly after he had an acute relapse with severe nausea and vomiting, general abdominal pain, marked weakness, and a falling blood pressure. He was treated with the cortical extract and glucose and showed a marked improvement in a few days. He was kept under observation and treatment was kept up in the hospital, and upon returning home, he received an injection daily and was in excellent condition. He returned for observation in October, 1931. The pigmentation may have been a little paler, the blood pressure 88/55. He again returned home apparently in good condition. However, 10 days later, he devel-
oped anorexia and was irritable, and although was reported improved somewhat after injection of larger doses of extract, died on the fifth day in an attack of coughing, dyspnoea which the attending physician thought similar to asthma and was relieved some with adrenalin.

Autopsy in this case also shows a complete absence of the cortical cells of the adrenal glands. (18)

During the attacks of adrenal insufficiency, gastrointestinal upsets are one of the common symptoms and also, it has been noted in experiments that there is an adrenal hypertrophy which takes place during pregnancy. Kemp (39), seeing a possible association between these two factors, suggested that the adrenal hypertrophy which takes place during pregnancy is not rapid enough to care for the extra load, and hence in early gestation there is a temporary and relative insufficiency which may be the cause of the early nausea and vomiting. The report of cases shows that by treatment with the cortical hormone, symptoms were relieved in two to three days. The treatment was continued for twelve to fourteen weeks and then discontinued without further trouble. The same treatment was tried in the later months of pregnancy with relatively good results. One case is reported.

Case #5: Mrs. S.M.S., age 24, Para 2. Last menses, November 20, 1931. Past history, one pregnancy with severe nausea and vomiting throughout pregnancy.

Present Illness: She first consulted the doctor, January 8, 1932. She complained of extreme nausea and vomiting many
times each day. Exactly like her first pregnancy. She was given adrenal cortex, nine grains each day (Armour). The first week, she had little improvement, thereafter, had a cessation of nausea and vomiting. In her own words, "I never felt better." She was symptom free until March 10, when she aborted. (39)


Present Illness: Patient consulted the doctor on February 10, 1932 for relief of the nausea and vomiting. Different remedies were tried without any effect. On February 20, administered suprarenal cortex, six grains three times a day, and within two days the nausea and vomiting had ceased. The dose was halved and she remained symptom free. (39)


Present Illness: This woman consulted the doctor on February 11, 1932 complaining of nausea and vomiting, vomiting several times daily, "felt miserable." She was given 18 grains of suprarenal cortex daily and at the end of three days, the nausea had disappeared and the vomiting ceased. She remained symptom free on three grains three times a day. (39)

The next case is one in the later months of Pregnancy.

Case #8: Mrs. R. K., age 22. Para 1. Last menses, June 26, 1931. Past history, she was always normal, healthy and athletic.
Present Illness: In the first trimester of pregnancy she was subject to nausea and vomiting. Her blood pressure ranged systolic 126 to 132, diastolic 70 to 80. Urine was normal. On January 4, she complained of severe headaches for some days, and had been nauseated and had vomited occasionally. She felt generally miserable. The blood pressure then went to 140/80, the urine showed a trace of albumin. She was sent home to bed with a low protein and salt free diet with suprarenal cortex, nine grains per day. After five days of treatment, her headache disappeared; the urine became normal and the blood pressure remained stationary during the remainder of her pregnancy, and she delivered normally the latter part of March, 1932. (39)

It must be kept in mind that a large psychic factor plays a part in nausea and vomiting of pregnancy, and the results from this treatment may be psychic, though these cases do lend strong support to Kemp's theory, and only need further trial.

Mendelson (44) made a recent report on the treatment of a case of progressive muscular atrophy with cortin. The progressive asthenia which is common to both progressive muscular atrophy and Addison's disease suggested the use of cortin and he thought it might relieve the symptoms. Although he got prompt and spectacular results, he warns to be mindful that one case is not conclusive.

Case #9: A man, age 30, Mexican, noticed his left arm and hand was weak in 1930. In July his weight was 131 pounds. The weakness gradually progressed with no intermissions up till he applied for treatment, July 1933. He found he could not lift kegs of nails.

Family history, negative. Past history, irrelevant.
Mumps, measles, typhoid. Complained of weight loss, transient pains affecting muscle groups, extreme weakness, inability to walk, insomnia and loss of sexual power.

Examination: Emaciated, weight, 103 pounds. He had dysphagia, dysarthria, atrophy of several major muscles of the trunk and thighs. No fibrillary contractions. Reflexes normal. Sphincters were all right. Wasserman negative. Red blood count was 5,500,000, hemoglobin, 90 percent, white cell count, normal. Urine and stool, negative. Blood pressure, 90/70.

Treatment consisted of the use of one cubic centimeter of cortin subcutaneously every day for ten days. No particular change was noted at the end of this course, so another course was tried, consisting of ten injections, one every three days. The patient said the pains began to leave, and could sleep well and the appetite increased. His sexual power was returning and he could walk without assistance. At the present time, (October, 1933, the weight was 1084 pounds, the blood pressure 110/80. He rides a bicycle several blocks, has gone duck hunting, walking five miles, and has a better outlook on life. (44)

The suprarenal cortical extract has been used for a few other conditions with variable success. One of the experiments that received the most attention a few years ago, was that of Coffey and Humber (10), where they believed they could cause a necrosis of malignant tumors. They injected the extract in graduated doses of one to 12 minums at definite intervals, and this was followed by a sloughing and the mass became necrotic and liquified, according to their reports. At autopsy, the areas showed necrosis in metastatic
growths, this was confirmed microscopically. The patients were re-
ported to have felt better, slept better and had an increase in
appetite and weight. The authors claim the cortex to have a destruc-
tive effect on malignant tissue without injuring normal tissue.
Only writings by these authors confirm this property of the cortex,
for there is one by Sugiura (60) which claims that the extract has
no effect on malignant growths when used in any of its forms, alco-
holic, ether, aqueous, or glycerine. Coffey and Humber, however,
bravely support their theory. They call attention to changes in the
cortex of people past 40, especially those who die of malignancy,
showing the cortex of the adrenal is most likely to become atrophied
and deficient.

Two recent reports have been made of the use of the
suprarenal cortex in the treatment of schizophrenia. This is still
in its experimental stage, and no conclusions were drawn, as to
whether this is characterized by adrenal insufficiency or whether the
results were nonspecific. Considerable improvement was noted in the
cases where it was tried, and upon withdrawal of the extract, they
returned to their initial condition. (20)(37).

Zwemer, (80), in his report of a preparation of an
extract, made note of two hundred babies that were suffering from
intestinal intoxication. Symptoms of adrenal insufficiency are
quite similar, and he concluded that some of the babies may show
improvement with the injection of the extract. Very small doses
were tried intramuscularly, and within twenty-four hours marked im-
provement was noted. Some of them died from other causes, but all
that were treated showed improvement, but one, and this was due to
loss of potency of the extract.
Rowntree, and others (54), made a report on some of the uses of the extract, some of which gave no results. Four cases of exophthalmic goiter were given the extract, and two cases showed a slight drop in the metabolic rate, but the others showed no change. In one case of myxodema, there was noted no change.

Six cases of anorexia nervosa were treated with the extract and studied, and in some there was an increase in the appetite, and the ability to take food, but some showed no effect. In five cases of asthenia associated with neuroasthenia or psychosis, treatment was of no avail. Cases of myasthenia gravis, diffuse myositis, postural hypotension or benign hypertension were treated without satisfactory results, and Rowntree concluded at that time (1931) that Addison's disease was the only one that could be successfully treated with the cortex. Other treatments are, as yet, still in the experimental and trial stage, and until time has allowed the results to develop from the other treatments, no definite statement can be made as to their success or failure.
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