patients who have a nephrotic type of edema, significant increases in the rate of excretion of chloride and water after the injection of a solution of acacia have been found.[8] Thus, curiously enough, the administration of a substance originally recommended on the assumption that it might increase colloid osmotic pressure appears to be therapeutically active because it facilitates the excretion of chloride and water by the kidney.

SUMMARY

The regimen of treatment herein presented for patients who have the nephrotic type of edema appears to be successful in 90 per cent of the severe types of cases. It consists of rest in bed, a salt-free, high protein diet, restriction of fluids, the oral administration of potassium nitrate and the intravenous injection of solutions of acacia. The latter can be given with comparative safety, provided preparation of the solution conforms with certain principles and provided the total dosage does not exceed the one recommended. Additional diuretic measures are seldom called for.

The favorable effect of administration of potassium nitrate is related definitely to its ability to increase the excretion of sodium chloride. Injections of solutions of acacia appear to augment the rate of excretion of sodium chloride and water as well and do not change significantly the colloid osmotic pressure of the serum.

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# DESOXYCORTICOSTERONE ACETATE THERAPY IN ADDISON'S DISEASE

## CLINICAL CONSIDERATIONS

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The synthesis of desoxycorticosterone [1] provided for the first time a practical method for preparing a supply of the crystalline form of the adrenal cortical factor adequate for clinical trial. The effectiveness of this compound in maintaining bilaterally adrenalectomized dogs in good condition despite a diet low in sodium chloride content has been reported.[2] The striking and beneficial effect of the synthetic type of the adrenal cortical principle in the treatment of patients with Addison's disease has also been described.[3] It appears likely that desoxycorticosterone acetate will be given extensive clinical trial as the use of this synthetic preparation greatly reduces the cost of treatment (table 1) and the relative stability and uniform potency of the compound permit more exact regulation of dosage than is possible with aqueous extracts of adrenal cortex. The marked potency of the crystalline substance, however, and the profound effects which attend its administration indicate the need for great care in its use. It is also apparent that the quantity of supplementary sodium chloride must be regulated carefully during treatment with desoxycorticosterone acetate. In contrast to treatment with aqueous extracts of adrenal cortex, which rarely produces overdosage phenomena when given in the quantity which most patients can afford, the continued administration of desoxycorticosterone acetate and added sodium chloride may result in the appearance of edema, hypertension and, in some instances, signs of congestive heart failure.[4]

During the past eighteen months thirty patients with classic signs and symptoms of Addison's disease have been treated with desoxycorticosterone acetate. Through the cooperation of physicians in other clinics throughout the country it has been possible to follow closely the results of treatment with the synthetic substance in thirty-five additional patients. Our purpose in the present communication is to discuss some of the more important clinical considerations which have arisen during the treatment of this group of sixty-five patients with Addison's disease.

### GENERAL CONSIDERATIONS

To date treatment with the synthetic compound has been limited to patients with classic signs and symptoms of Addison's disease, i. e. an increase in pigmentation, hypotension, asthenia, loss of weight and gastrointestinal symptoms. In many of these cases critical episodes of acute adrenal insufficiency have occurred, thus substantiating the diagnosis. The sodium chloride deprivation test described by Cutler, Power and Wilder [5] has been employed as an additional aid in diagnosis. However, as these authors indicate, the test should be carried out with extreme caution. This note of warning was amply confirmed, as an adrenal crisis was precipitated in case 19 on the third morning of the test.

It is possible for some patients with Addison's disease to be maintained in fair health by means of sodium chloride therapy alone. However, a return to normal activity on this regimen alone appears to be the exception rather than the rule. It would seem to be both desirable and advisable to provide desoxycorticosterone therapy for all patients with Addison's disease who cannot be restored to normal activity by means of added sodium chloride therapy and a diet of low potassium content.

Although experimental evidence [6] indicates that atrophy of the normal adrenal cortex may follow excessive desoxycorticosterone therapy in normal animals, it is not likely that this fact is of clinical significance since well marked signs and symptoms of Addison's disease rarely are observed until extensive destruction of adrenal cortical tissue has occurred. At present it

8. Goudsmit, Arnoldus, Jr.; Binger, M. W., and Keith, N. M.: Unpublished data.

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From the Chemical Division, Medical Clinic, and the Department of Surgery, the Johns Hopkins University and Hospital.

Protocols of patients 1, 2, 4, 5, 6, 7, 8, 9, 10, E. W. and J. P. have been published (Thorn, Howard, Emerson and Firor.[3] Thorn, Howard and Emerson [10]).

Drs. Kendall Emerson Jr., R. Palmer Howard and George Koepf, Miss Mildred Caldwell, supervisor of the metabolism ward, Miss Elizabeth Olsen, dietitian in charge of the metabolism ward, and Mrs. Florence White, of the Biochemical Laboratory of the John Hopkins Hospital, gave assistance and continued cooperation.

1. Steiger, M., and Reichstein, T.: Desoxycorticosterone (21-oxy-progesteron) aus 3-oxy-ätio-cholen-saure), Helvet. chim. acta **20:** 1164, 1937.

2. Thorn, G. W.; Engel, L. L., and Eisenberg, Harry: The Effect of Corticosterone and Related Compounds on the Renal Excretion of Electrolytes, J. Exper. Med. **68:** 161 (Aug.) 1938; Treatment of Adrenal Insufficiency by Means of Subcutaneous Implants of Pellets of Desoxycorticosterone Acetate (a Synthetic Adrenal Cortical Hormone), Bull. Johns Hopkins Hosp. **64:** 155 (March) 1939. Thorn and Eisenberg.[8]

3. Thorn, G. W.; Howard, R. P.; Emerson, Kendall, Jr., and Firor. W. M.: Treatment of Addison's Disease with Pellets of Crystalline Adrenal Cortical Hormone (Synthetic Desoxycorticosterone Acetate) Implanted Subcutaneously, Bull. Johns Hopkins Hosp. **64:** 339 (May) 1939. Cleghorn, R. A.; Fowler, J. L. A., and Wenzel, J. S.: The Treatment of Addison's Disease by Synthetic Adrenal Cortical Hormone (Desoxycorticosterone Acetate), Canad. M. A. J. **41:** 226 (Sept.) 1939. Ferrebee, Ragan, Atchley and Loeb.[4] Thorn, Howard and Emerson.[10]

4. Ferrebee, J. W.; Ragan, Charles; Atchley, D. W., and Loeb, R. F.: Desoxycorticosterone Esters: Certain Effects in the Treatment of Addison's Disease, J. A. M. A. **113:** 1725 (Nov. 4) 1939.

5. Cutler, H. H.; Power, M. H., and Wilder, R. M.: Concentrations of Chloride, Sodium and Potassium in Urine and Blood, J. A. M. A. **111:** 117 (July 9) 1938.

6. Ingle, D. J.: The Effect of Administering Large Amounts of Cortin on the Adrenal Cortices of Normal and Hypophysectomized Rats, Am. J. Physiol. **124:** 369 (Nov.) 1938.

would seem to be unjustifiable to withhold substitution therapy from a patient with Addison's disease if sodium chloride therapy alone was ineffective in completely restoring him to normal activity.

### DOSAGE AND MODE OF ADMINISTRATION

A solution of desoxycorticosterone acetate in oil [7] in which 5 mg. of crystalline substance was contained in 1 cc. of sesame oil was used in these studies. Experimental studies [8] indicated that a prolonged effect (twenty-four hours) followed a single intramuscular injection of the compound in oil. The desoxycorticosterone acetate requirement for the majority of patients with Addison's disease appeared to be less than 6 mg. daily. During a crisis or during a period of increased stress from 10 to 25 mg. daily was required.

Patients with Addison's disease can be treated successfully either with desoxycorticosterone acetate alone or with this factor supplemented by sodium chloride therapy. It is possible that desoxycorticosterone treatment alone would result in a lower incidence of undesirable complications, i. e. edema, hypertension and possibly myocardial insufficiency. However, added sodium chloride therapy greatly reduces the desoxycorticosterone requirement and hence the cost of treatment. If care is used in regulating the quantity of added sodium chloride, overdosage phenomena rarely occur.

TABLE 1.—*Approximate Cost of Equivalent Quantities of Adrenal Cortical Principle*

| Preparation | Daily Requirement | Approximate Cost per Year * |
|---|---|---|
| Aqueous adrenal cortex extract.... | 8.0 cc. | $900 |
| Synthetic compound in oil..... | 2.6 mg. | 140 |
| Pellets of synthetic compound.... | 1.8 mg. | 98 † |

* Prices quoted to patients by the pharmacy of the Johns Hopkins Hospital, Dec. 15, 1939.

† Since pellets of the synthetic compound are not yet available commercially, the cost of these tablets has been estimated from the price of crystalline desoxycorticosterone acetate in oil.

A simple plan for instituting treatment consists in giving from 6 to 8 Gm. of added sodium chloride by mouth and from 2 to 5 mg. of desoxycorticosterone acetate in oil by injection intramuscularly once daily. The most striking immediate effects of treatment with the synthetic factor are rapid gain in weight associated with retention of sodium, chloride and water, marked increase in plasma volume (hemodilution) and striking improvement in the clinical condition of the patient. Failure to gain weight within forty-eight to seventy-two hours after desoxycorticosterone acetate therapy is instituted is the first indication of insufficient dosage. Too rapid gain in weight (more than 0.5 Kg. daily during the first week of treatment and more than 0.3 Kg. daily subsequently), if continued, indicates overdosage. This will result in the appearance of edema if the dose of desoxycorticosterone or sodium chloride is not reduced. The maximum rise in blood pressure may not occur until treatment has been continued for from four to sixteen weeks.

In some cases treatment with small quantities of the synthetic compound (1 or 2 mg. daily) in addition to from 6 to 8 Gm. daily of added sodium chloride may result in the appearance of edema. Under these circumstances the sodium chloride therapy should be reduced gradually and if necessary entirely discontinued. The optimum daily maintenance dose of desoxycorticosterone acetate appears to be that which will maintain body weight without resulting in excessive weight gain, appearance of edema or too great elevation in blood pressure. It is obvious that overwork, excessive fatigue, exposure to heat or cold or the presence of infection may greatly increase the requirement temporarily.

In some cases complications which exist at the onset of treatment favor the accumulation of excessive quantities of sodium, chloride and water before the optimum therapeutic dose of desoxycorticosterone acetate is attained, i. e. case 4, hypoproteinemia, case 19, phlebitis of the left leg, case 15, myocardial damage. Under these conditions it is advisable to restrict the intake of sodium chloride and to increase slowly the dose of the synthetic compound.

In general, smaller quantities of desoxycorticosterone acetate are indicated in the treatment of patients past middle life since the great increase in blood volume, the rise in blood pressure and the increased physical activity which follow the institution of therapy place a considerable additional load on the cardiovascular system rather suddenly. It is suggested that the activity of patients in the advanced age group, or patients with complicating cardiovascular disease, should be restricted during the first few weeks of treatment.

### TREATMENT OF ADRENAL CRISIS

Since the maximum effect from a single intramuscular injection of desoxycorticosterone acetate in oil does not occur until from six to twelve hours after injection, it is desirable in the treatment of adrenal crisis to supplement intramuscular injections of the synthetic compound with intravenously and subcutaneously administered aqueous extract. The following technic has been used successfully:

*First Day.*—A. Immediately on admission to the hospital the patient is placed in a warm bed and given 0.5 cc. of a solution of epinephrine hydrochloride subcutaneously if the systolic blood pressure is less than 70 mm. of mercury. At the same time (*a*) from 25 to 35 mg. of desoxycorticosterone acetate in oil is injected intramuscularly, the total quantity being divided and injected in three or four different sites; (*b*) 25 cc. of aqueous extract is injected subcutaneously in divided doses, and (*c*) 25 cc. of aqueous extract is added to a venoclysis of 1,000 cc. of 1.5 per cent sodium chloride solution and 1,000 cc. of 5 to 10 per cent dextrose solution, which is administered slowly. Since hypoglycemia frequently complicates a crisis, great care is taken to maintain a normal blood sugar level.[9]

B. During the second twelve hour period from 500 to 1,000 cc. of physiologic solution of sodium chloride

7. The desoxycorticosterone acetate in sesame oil (percorten) used in this study was supplied by Ciba Pharmaceutical Products, Inc., through Dr. E. Oppenheimer. It has not yet been considered by the Council on Pharmacy and Chemistry of the American Medical Association.

8. Thorn, G. W., and Einsenberg, Harry: Studies on Desoxycorticosterone: A Synthetic Adrenal Cortical Hormone, Endocrinology **25**: 39 (July) 1939.

9. Dextrose tolerance curves show (Thorn, Koepf, Kuhlmann and Olsen [18]) that from three to six hours after the administration of dextrose patients with Addison's disease may have rather marked hypoglycemic reactions, if additional carbohydrate is not provided. Reactions are particularly likely to occur after parenteral administration of dextrose. Thus a complicated situation arises in which dextrose solutions given to correct the hypoglycemic state may in turn precipitate a hypoglycemic reaction unless appropriate preventive measures are taken. It is possible that some of the sudden deaths reported in the literature which occurred after an initial satisfactory response may be accounted for by this mechanism. It seems highly important to supply an adequate and continuous source of carbohydrate for all patients during the first forty-eight hours of crisis.

and from 500 to 1,000 cc. of 5 to 10 per cent dextrose solution are slowly given intravenously. If they are tolerated, the patient is encouraged to drink ginger ale and fruit juice. It is not necessary to give additional desoxycorticosterone acetate at this time.

*Second Day.*—From 10 to 20 mg. of desoxycorticosterone acetate in oil is given intramuscularly and 1,000 cc. of physiologic solution of sodium chloride and 1,000 cc. of 5 to 10 per cent dextrose solution are given intravenously. Frequent small feedings of readily available carbohydrate are given and the patient is encouraged to drink ginger ale and fruit juice. In the event that food and liquids are not tolerated by mouth, great care is taken to provide for an adequate carbohydrate intake by continued parenteral administration of dextrose solution.

*Third Day.*—From 5 to 15 mg. of desoxycorticosterone acetate in oil is given intramuscularly and, if possible, from 3 to 6 Gm. of sodium chloride (1 Gm. enteric coated tablets) is given by mouth. If sodium chloride is not tolerated by mouth an equivalent quantity of sodium chloride is given parenterally. The appearance of edema indicates excessive sodium chloride and desoxycorticosterone therapy, and the dosage of one or both of these medications is then reduced promptly.

## REPORT OF CASE

CASE 18.—*History.*—R. M., a married housewife, aged 34, was admitted to the Johns Hopkins Hospital Aug. 14, 1939, with a diagnosis of Addison's disease. Her present illness began in the summer of 1937, at which time she noted loss of strength and attacks of weakness associated with nausea and vomiting. During the summer of 1938 brownish pigmentation of the skin developed over the hands and neck. Since the onset of illness she had lost 9.1 Kg. of weight. Because of frequent attacks of sore throat, a tonsillectomy was performed on June 19, 1939. After the tonsillectomy the patient did very poorly; nausea and vomiting occurred and were followed by extreme prostration. At this time a diagnosis of Addison's disease was made and the administration of added sodium chloride and daily injections of desoxycorticosterone acetate was followed by rapid improvement. She was transferred to the Johns Hopkins Hospital August 14, for implantation of pellets of desoxycorticosterone acetate after two months' treatment with daily injections of desoxycorticosterone acetate in oil and sodium chloride therapy.

*Physical Examination.*—The patient was rather thin but not acutely ill. Her temperature was 99.8 F., pulse rate 96 and respiratory rate 20 per minute. At this time the blood pressure was 98 mm. of mercury systolic, 60 mm. diastolic. The skin showed areas of brownish pigmentation over the hands, arms, neck, thorax, dorsum of the feet and to a lesser extent on the face. Some pigmentation was present about the margin of the lower lip. Examination of the lungs, heart and abdomen revealed no abnormality.

*Laboratory Data.*—The red blood cell count was 4,220,000, hemoglobin content 90 per cent (13.8 Gm.) and white blood cell count 7,720 with 49 per cent polymorphonuclears, 42 per cent lymphocytes and 9 per cent monocytes. The volume of packed red cells was 35 per cent. The blood Wassermann reaction was negative. The sedimentation rate was 20 mm. in one hour, corrected. The blood nonprotein nitrogen level was 23 mg., blood sugar 79 mg., the plasma carbon dioxide-combining power 54.1 volumes per cent and the total serum protein 6.8 Gm. per hundred cubic centimeters. The serum chloride value was 108.4 milliequivalents, serum sodium 141.3 milliequivalents and serum potassium 3.6 milliequivalents per liter. The x-ray appearance of the heart, lungs and abdomen was normal. The electrocardiogram showed an inverted T wave in the chest lead.

After the oral administration of 1.75 Gm. of dextrose per kilogram of body weight the following blood sugar values were noted: fasting 80 mg., one-half hour after dextrose 125 mg., one hour 100 mg., two hours 90 mg., three hours 75 mg. and four hours 75 mg. per hundred cubic centimeters.

*Desoxycorticosterone Acetate Treatment.*—Treatment with the synthetic product was instituted at a time when the patient was very weak, nauseated and vomiting. The blood pressure was 60 systolic, 40 diastolic, and the heart rate was rapid, the heart sounds being distant. Repeated infusions of 5 per cent dextrose and 1.5 per cent sodium chloride were given, supplemented by fruit juice and ginger ale given orally in small quantities. Ten mg. of desoxycorticosterone acetate was injected intramuscularly once daily. As soon as possible the parenterally administered sodium chloride was replaced by tablets of sodium chloride (1 Gm. enteric coated) given by mouth. One tablet was given three times daily and later two tablets three times daily, i. e. a total of 6 Gm. daily. On this regimen the patient gained weight rapidly, her strength improved and her blood pressure was increased to 94 systolic, 60 diastolic. Ten days after treatment was instituted, however, edema of the extremities and some puffiness of the face were noted, accompanied by a rather severe headache. It was evident that excessive sodium chloride and water retention had occurred. For this reason the daily dose of desoxycorticosterone acetate in oil was reduced to 5 mg. daily, the dose of added sodium chloride being maintained at 6 Gm. daily. Later the sodium chloride was reduced to 3 Gm. daily and the desoxycorticosterone acetate to 4 mg. daily. It was observed that the patient could be maintained in very good condition on this regimen.

Approximately two months after treatment with daily injections of the synthetic compound in oil had been instituted, the patient was admitted to the Johns Hopkins Hospital for implantation of pellets of crystalline desoxycorticosterone acetate. At this time her blood pressure was 98 systolic, 60 diastolic, and her weight 52.5 Kg. and she was greatly improved clinically. Treatment at this time consisted of a single daily injection of 4 mg. of desoxycorticosterone acetate in oil and 3 Gm. of added sodium chloride in addition to a diet of high sodium chloride content. At this time eight pellets of crystalline desoxycorticosterone acetate (approximately 125 mg. each) were implanted in the subcutaneous tissues beneath the right scapula. The daily injections of the substance were discontinued but the sodium chloride therapy was continued.

TABLE 2.—*Blood Sugar Values Following the Oral Administration of Dextrose* *

| Time | Before Treatment | Desoxycorticosterone Acetate Treatment (6 Months) |
|---|---|---|
| Fasting | 80 | 84 |
| ½ hour | 125 | 160 |
| 1 hour | 100 | 141 |
| 2 hours | 90 | 118 |
| 3 hours | 75 | 79 |

* The dose was 1.75 Gm. of dextrose per kilogram of body weight. Values indicate milligrams per hundred cubic centimeters.

After the implantation of the pellets the patient continued to do well. At the time of discharge, August 25, the blood pressure was 100 systolic, 68 diastolic, and she had gained 2.5 Kg. of weight since admission. Laboratory data at the time of discharge were as follows: The red blood cell count was 3,980,000, hemoglobin level 82 per cent (12 Gm.), white blood cell count 7,480 and the volume of packed red blood cells 35 per cent. The blood nonprotein nitrogen level was 24 mg., the blood sugar 80 mg., the plasma carbon dioxide-combining power 52.2 volumes per cent and the total serum protein 6.2 Gm. per hundred cubic centimeters. The serum concentration of chlorides was 105.6 milliequivalents, of sodium 140 milliequivalents and of potassium 4 milliequivalents per liter. The electrocardiogram showed less inversion of the T wave in the chest lead than on admission.

At present, six months after treatment with the synthetic compound was instituted, the patient is in very good condition and is able to carry on all her usual household duties. She had gained a total of 7 Kg. in weight and the blood pressure had increased from 98 systolic, 60 diastolic, to 130 systolic, 90

diastolic. One month after the pellets were implanted, the 3 Gm. of added sodium chloride was discontinued. Present therapy consists solely of the pellets of desoxycorticosterone acetate which were implanted in August 1939.

COMPLICATIONS

1. In two cases (1 and 6) intramuscular injections of desoxycorticosterone acetate in sesame oil were associated with constitutional symptoms (fever and malaise) and localized redness, pain and tenderness at the site of the injections. It was shown that these reactions were due to the injection of oil of sesame and not to the desoxycorticosterone acetate.[10] In these cases the necessity for daily injections of the compound in oil was obviated by subcutaneously implanting pellets of the crystalline form of the material.

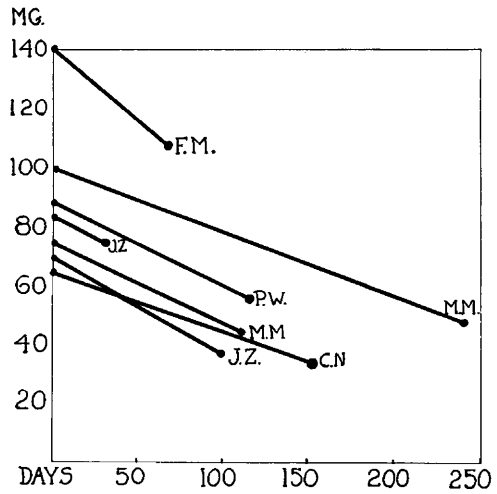


Fig. 1.—Decrease in the weight of pellets in patients. The quantity of desoxycorticosterone acetate observed daily from a pellet weighing approximately 100 mg. was found to be 0.29 mg. (mean).

2. Edema associated with headache may result from an overdose of desoxycorticosterone acetate but more frequently results from combined treatment with this substance and sodium chloride. This complication is most likely to occur during the first two or three weeks of treatment when the optimum daily maintenance dose is being ascertained. The edema disappears rapidly after the reduction of the dose of sodium chloride or the synthetic compound or after the addition of potassium salts to the diet, i. e. a 10 per cent solution of potassium citrate from 10 to 20 cc. added to fruit juice and given two or three times daily.

3. Occasionally after a continued period of desoxycorticosterone acetate therapy during which the patient's plasma volume, weight, blood pressure and activity have been greatly increased, dyspnea associated with signs of pulmonary edema may be noted. This complication is most likely to occur in cases in which there is some evidence of preexisting myocardial damage or vascular disease and may be avoided if great care is exercised in the regulation of treatment and if activity is restricted during the early period of rehabilitation. Treatment consists in absolute bed rest, digitalization, immediate withdrawal of sodium chloride therapy and, if necessary, a reduction in the dose of desoxycorticosterone acetate.

4. Hypertension may be noted following continued treatment with sodium chloride and the adrenal principle. In cases of Addison's disease in which hypertension antedated the onset of symptoms of Addison's disease, the blood pressure is particularly likely to return to a high level after adequate therapy. The elevated blood pressure responds readily to withdrawal of added sodium chloride, to reduction in the dose of the adrenal factor or to the additional potassium medication.

5. Hypoglycemia may be observed following a prolonged fast in patients treated with desoxycorticosterone acetate. The presence of complicating infection greatly increases the likelihood of hypoglycemic reactions. Until more is known about the nature of the disturbance in carbohydrate metabolism, it is desirable to provide a diet high in readily available carbohydrate for all patients with Addison's disease.

6. The continued administration of excessive quantities of desoxycorticosterone acetate and added sodium chloride may result in an abnormal lowering of the serum concentration of potassium. This is particularly likely to occur if large quantities of dextrose solution are given simultaneously. In case 6 on two occasions an abnormal lowering of the serum concentration of potassium was associated with muscular weakness and transient paralysis involving the extensor muscles of the neck, hands and feet. This patient had been given large quantities of the synthetic compound (25 mg. daily) in addition to intravenous sodium chloride and dextrose solutions before and after a nephrectomy. The abrupt onset and transient nature of the paralysis as well as the complete recovery suggest an analogy between these episodes and those noted in patients with familial periodic paralysis in which the serum potassium level has also been observed to be low during an attack.[11] Recent examination of this patient reveals no muscular weakness or incapacity. Such untoward

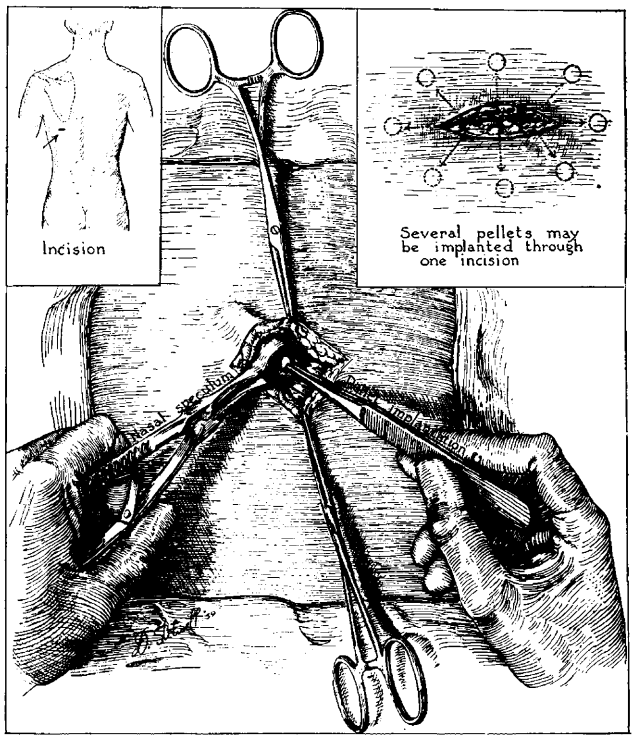


Fig. 2.—Technic of pellet implantation.

10. Thorn, G. W.; Howard, R. P., and Emerson, Kendall, Jr.: Treatment of Addison's Disease with Desoxycorticosterone Acetate, a Synthetic Adrenal Cortical Hormone (Preliminary Report), J. Clin. Investigation **18**: 449 (July) 1939.

11. Aitken, R. S.; Allott, E. N.; Castleden, L. I. M., and Walker, Mary: Observations on Case of Familial Periodic Paralysis, Clin. Sc. **3**: 47 (July) 1937.

effects may be obviated easily by properly regulating the dose of desoxycorticosterone acetate. Added potassium citrate or foods rich in potassium (bananas, prunes and raisins) may also be given with advantage.

7. The close chemical relationship between desoxycorticosterone and progesterone suggests that desoxycorticosterone acetate treatment might possibly result in progestational changes in female patients with Addison's disease. To date, however, no abnormality in the menstrual cycle has been observed as the result of treatment with the synthetic adrenal principle. In several patients increased turgor of the breasts has been noted after continued treatment. It appears probable that this change may be accounted for in part by the increased accumulation of extracellular fluid.

It is to be noted that most of the complications which have been enumerated may be avoided if reasonable care is exercised in the administration of desoxycorticosterone acetate and sodium chloride.

### SUBCUTANEOUSLY IMPLANTED PELLETS OF CRYSTALLINE DESOXYCORTICOSTERONE ACETATE [12]

In addition to daily intramuscular injections of the drug in oil it has been observed [8] that subcutaneously implanted pellets of crystalline desoxycorticosterone acetate provide an efficacious and very efficient method of administration. The advisability of implantation may be considered after a patient has been maintained in good condition for one month or more by means of daily injections of the medicament in oil. Pellets should be implanted only after careful clinical control has permitted the daily requirement of the drug to be determined accurately. It requires at least four to eight weeks to establish with certainty the optimum daily dose of the substance in oil.

1. *Calculation of Pellet Requirement.*—The pellet requirement of desoxycorticosterone acetate is calculated from the optimum daily maintenance dose, one pellet of from 100 to 150 mg. being substituted for each 0.4 to 0.5 mg. of the material necessary for maintenance. The daily maintenance dose of desoxycorticosterone acetate in oil is determined during a period in which the patient is receiving a constant quantity of added sodium chloride (from 4 to 8 Gm. daily). It is desirable to use sodium chloride therapy if pellets are to be implanted, since at any future date reduction or withdrawal of the sodium chloride provides a very convenient means of balancing any excess of desoxycorticosterone acetate. Pellets weighing from 100 to 150 mg. should provide effective therapy for from nine to twelve months (fig. 1).

2. *Technic of Pellet Implantation.*—The infrascapular region has been found to be a convenient site for the implantation of the pellets. It is imperative that strict aseptic technic be followed because of the susceptibility of addisonian patients to pyogenic infections. In all the cases reported in this paper the implantations have been carried out in the general operating rooms of the hospital.

The operative field is carefully prepared with iodine and alcohol. The site of the incision and the surrounding subcutaneous tissue are infiltrated with procaine hydrochloride 1:200. A transverse incision (from 3 to 7 cm. in length) is made a few centimeters below the inferior spine of the scapula and extending toward the posterior axillary line. A number of pockets are then made in the subcutaneous fat (fig. 2). These radiate in all directions from the margins of the cutaneous incision and average 4 cm. in depth. After hemostasis has been obtained, each opening in the subcutaneous fat is held far enough apart by a nasal dilator to permit a pellet to gravitate to the bottom of the pocket without the use of force. This is important, for if the opening is narrow the operator may crush the pellet when trying to insert it. If it is desired to mark a particular pellet, one can easily do so by attaching a silver clip to it with a fine silk suture. After all the pellets have been placed, the wound is closed with subcuticular sutures of fine black silk. It is possible to insert as many as fifteen pellets through a single incision. In no instance has there been suppuration, discernible inflammatory reaction or extrusion of a pellet.

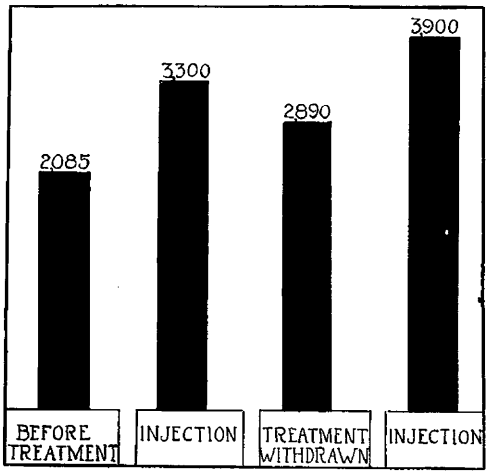


Fig. 3.—Changes in plasma volume of F. M. which occurred during injection treatment with the synthetic adrenal cortical factor. Treatment was withdrawn for seventy-two hours. The figures represent cubic centimeters.

### RESULTS OF TREATMENT

Desoxycorticosterone acetate treatment (either daily oil injections or subcutaneous implantation of crystalline pellets) resulted in striking changes in patients with Addison's disease, i. e. (*a*) increase in weight, (*b*) increase in plasma volume (fig. 3), (*c*) positive sodium and chloride balance, (*d*) increased renal excretion of potassium and phosphate, (*e*) restoration of plasma concentrations of sodium, chloride, potassium and nonprotein nitrogen to normal levels, (*f*) improved muscular strength and sense of well-being and (*g*) elevation of blood pressure. These changes have been described in detail in a previous communication. Patients were not restored completely to normal activity until the abnormality in the serum concentration of electrolytes had been corrected. However, it is to be noted that the restoration of the concentration of sodium, chloride and potassium of the serum to normal values was not always associated with the complete disappearance of clinical symptoms (table 3).

At the present time twenty of thirty consecutively treated patients in this study are leading a life of normal activity and are working or able to work regularly (table 3). Two additional patients (J. P. and V. R.) were treated with daily injections of desoxy-

12. The crystalline desoxycorticosterone acetate used in this investigation has been prepared and pressed into pellets in our laboratory and more recently by Ciba Pharmaceutical Products, Inc. Although the results obtained with tablet-shaped pellets weighing approximately 125 mg. are very encouraging, the pellets will not be made available commercially until further clinical experience has accumulated to justify the conclusion that these pellets and this new therapeutic procedure are safe. For purposes of clinical investigation it is suggested that the implantation treatment should be undertaken only with uniformly pressed, shaped and assayed sterile pellets after a careful study of the case has indicated the exact medicinal requirement.

corticosterone acetate for short periods (ten to forty-five days respectively) with considerable clinical improvement. However, since it was possible to maintain both of these patients in good condition by means of added sodium chloride alone, desoxycorticosterone acetate therapy has not been continued.

Six patients in the group of thirty are greatly improved but are as yet unable to resume all normal activity. In two of these patients there exists a complication which limits the extent of improvement which might otherwise be expected: i. e., extensive healed pulmonary tuberculosis (patient 20) and active tuberculous infection of one kidney (patient 7).

(10 mg. daily) and added sodium chloride (10 Gm. daily) resulted in striking improvement, and the patient was maintained in good condition. Subsequently she was found to be pregnant. In view of the greatly improved clinical condition following continued synthetic desoxycorticosterone acetate therapy, the advisability of a therapeutic abortion was considered. Dilation and curettage of the uterus were performed during the third month of pregnancy. Postoperatively pneumonia developed, from which she completely recovered. The presence of pelvic phlebitis further complicated the convalescence. Throughout this period of rather severe illness her blood pressure did not fall below 95 mm. and she showed no evidence of adrenal insufficiency. During the fourth week of convalescence she had a chill, followed by high fever and

TABLE 3.—*Observations on Thirty Patients*

| Patient | Sex | Age | Duration of Symptoms, Years | Severity of Disease | Probable Etiology | Complications | Blood Pressure, Mm. Hg | | Body Weight, Kg. | | Desoxycorticosterone Acetate Therapy | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Initial* | Subsequent | Initial* | Subsequent | Daily Injections, Days | Implanted Pellets, Days | Total Duration of Therapy, Days |
| 1. P. W. | ♂ | 34 | 7 | ++++ | Nontuberculous | 0 | 95/60 | 128/ 84 | 51.0 | 58.2 | 106 | 338 | 444 |
| 2. M. M. | ♀ | 27 | 3 | ++++ | Nontuberculous | 0 | 85/72 | 130/ 92 | 51.3 | 54.0 | 0 | 444 | 444 |
| 3. E. V. | ♂ | 39 | 4 | ++++ | Nontuberculous | 0 | 94/60 | 145/ 90 | 54.4 | 62.8 | 206 | 237 | 443 |
| 4. C. N. | ♀ | 34 | 3 | +++ | Nontuberculous | 0 | 94/60 | 132/ 96 | 55.9 | 63.2 | 84 | 353 | 437 |
| 5. F. M. | ♂ | 32 | 3 | +++ | Nontuberculous | 0 | 92/60 | 160/105 | 61.2 | 66.0 | 147 | 288 | 435 |
| 6. J. Z. | ♂ | 19 | 3 | ++++ | Tuberculous | Urogenital tuberculosis (active) | 85/60 | 120/ 90 | 39.3 | 45.5 | 91 | 338 | 429 |
| 7. A. S. | ♂ | 32 | 4 | +++ | Tuberculous | Urogenital tuberculosis (active) | 104/68 | 136/ 70 | 57.4 | 57.2 | 129 | 264 | 393 |
| 8. J. S. | ♂ | 29 | 3 | +++ | Nontuberculous | 0 | 92/70 | 135/ 90 | 55.2 | 70.4 | 207 | 221 | 428 |
| 9. J. H. | ♂ | 22 | 2 | ++++ | Nontuberculous | 0 | 100/60 | 126/ 85 | 63.2 | 67.5 | 11 | 324 | 335 |
| 10. D. B. | ♂ | 33 | 2 | ++++ | Nontuberculous | 0 | 108/70 | 131/ 90 | 64.7 | 73.6 | 11 | 320 | 331 |
| 11. I. B. | ♀ | 45 | 5 | +++ | Nontuberculous | Hepatic disease | 110/74 | 170/100 | 48.0 | 48.4 | 35 | 264 | 299 |
| 12. J. D. | ♂ | 68 | 2 | +++ | Nontuberculous | Hypertrophic arthritis | 108/70 | 120/ 80† | 62.5 | 69.0† | 50 | ... | 50 |
| 13. S. W. | ♀ | 54 | 2 | +++ | Nontuberculous | Hypertrophic arthritis | 120/78 | 148/ 85 | 58.5 | 64.4 | 13 | 257 | 270 |
| 14. R. W. | ♂ | 56 | 2 | ++ | Nontuberculous | Hypertrophic arthritis | 108/70 | 138/ 80 | 71/2 | 72.7 | 28 | 217 | 245 |
| 15. Y. E. | ♀ | 38 | 2 | ++++ | Nontuberculous | 0 | 102/74 | 155/ 90 | 51.9 | 52.9 | 6 | 213 | 219 |
| 16. W. B. | ♂ | 20 | 2 | +++ | Nontuberculous | Pneumonia | 92/74 | 132/ 94 | 41.5 | 41.5 | 10 | 202 | 212 |
| 17. A. H. | ♀ | 37 | 3 | ++++ | Nontuberculous | 0 | 90/58 | 126/ 82 | 40.0 | 45.6 | 55 | 156 | 211 |
| 18. R. M. | ♀ | 34 | 2 | ++++ | Nontuberculous | 0 | 60/40 | 132/ 95 | 49.6 | 56.0 | 47 | 136 | 183 |
| 19. F. H. | ♂ | 22 | 1 | ++++ | Nontuberculous | 0 | 95/54 | 140/ 90 | 59.5 | 70.0 | 29 | 95 | 124 |
| 20. A. T. | ♂ | 48 | 3 | +++ | Tuberculous | Preexisting hypertension | 118/80 | 166/100 | 60.0 | 64.1 | 14 | 107 | 121 |
| 21. I. H. | ♀ | 34 | 3 | ++++ | Tuberculous | 0 | 108/70 | 124/ 88 | 53.0 | 56.9 | 25 | 47 | 72 |
| 22. C. E. | ♂ | 67 | 4 | ++++ | Nontuberculous | 0 | 104/78 | 130/ 90 | 51.2 | 54.4 | 19 | 47 | 66 |
| 23. A. K. | ♀ | 30 | 1 | ++++ | Nontuberculous | Pregnancy | 90/60 | 120/ 60† | 54.8 | 59.4† | 60 | .. | 60 |
| 24. F. G. | ♀ | 29 | 2 | ++ | Tuberculous | 0 | 104/65 | 116/ 80 | 46.8 | 48.7 | 221 | 16 | 237 |
| 25. D. W. | ♀ | 26 | 7 | +++ | Nontuberculous | 0 | 105/70 | 115/ 75 | 60.0 | 61.0 | 73 | .. | 73 |
| 26. M. B. | ♀ | 31 | 4 | ++++ | Nontuberculous | 0 | 90/66 | 105/ 66 | 49.4 | 51.0 | 25 | 26 | 51 |
| 27. C. C. | ♀ | 41 | 2 | +++ | Nontuberculous | 0 | 124/76 | 154/110 | 43.1 | 44.6 | 122 | 16 | 138 |
| 28. M. P. | ♀ | 34 | 2 | ++ | Nontuberculous | 0 | 102/80 | 115/ 80 | 71.8 | 71.5 | 101 | .. | 101 |
| 29. S. P. | ♂ | 27 | 1 | ++++ | Nontuberculous | 0 | 120/75 | 140/100 | 70.9 | 71.6 | 76 | 15 | 91 |
| 30. H. M. | ♂ | 45 | 3 | ++ | Nontuberculous | 0 | 96/54 | 110/ 60 | 66.0 | 70.8 | 28 | .. | 28 |

* Values at the time desoxycorticosterone acetate treatment was substituted for some other form of therapy.
† Value fourteen days after treatment with the synthetic adrenal cortical principle was instituted.

The clinical condition of three of the remaining six patients (11, 15 and 27) has been improved, but it is still necessary for them to lead a life of restricted activity (table 4, summary). In addition patient 22, aged 67, who was admitted to the hospital in crisis, is improved but as yet he is unable to do more than be up and about his bedroom despite continued treatment for ten weeks. In all these cases the blood pressure has been restored to levels which are normal or in some instances higher than normal, and the concentration of electrolytes in the blood serum is within normal range (table 3).

Patient 23 died during the course of an intercurrent infection. She was first observed during a typical crisis of adrenal cortical insufficiency. Treatment with desoxycorticosterone acetate

constitutional symptoms. At this time many colonies of colon bacilli were found in the blood stream, and the patient ultimately succumbed to a colon bacillus septicemia. Autopsy revealed pelvic peritonitis as well as an almost complete absence of adrenal cortical tissue.

It was thought that this patient had been restored to health from an adrenal crisis and maintained in good condition with the synthetic adrenal factor and added sodium chloride. She had also been maintained in relatively good condition during a major operation and for a period of three weeks postoperatively, despite unusual and severe complications, only to succumb finally to a colon bacillus septicemia.

Patient 12, a white man aged 68, was benefited by the synthetic adrenal principle during his residence in the hospital. However, extensive osteo-arthritic changes in his knees, hips

and shoulders confined him to bed. Withdrawal of the drug precipitated a relapse despite the continued administration of added sodium chloride. Resumption of desoxycorticosterone treatment again resulted in improvement. After returning to his home in Kentucky he discontinued the synthetic adrenal factor despite urgent medical advice to the contrary. Approximately two months after discontinuing treatment with the synthetic compound he died, apparently of adrenal insufficiency. Permission for postmortem examination was not obtained.

### BLOOD PRESSURE

A marked increase in blood pressure was observed in all of the patients treated with desoxycorticosterone acetate (either daily injections of the substance or pellets implanted subcutaneously). Particularly noteworthy was the appreciable rise in the diastolic pressure. It is of some interest that in most cases there occurred first a considerable increase in plasma volume (hemodilution) unaccompanied by any significant change in blood pressure. Later, after from four to twelve weeks of continued desoxycorticosterone and sodium chloride therapy the rise in blood pressure was marked in many instances. In most cases a rise in blood pressure was associated with evidence of marked clinical improvement. In some instances, however, hypertensive levels were attained without complete restoration of the patients to full normal activity.

Myocardial failure occurred in two cases (15 and 11) six weeks and twelve weeks respectively after treatment with the synthetic product (approximately 10 mg. daily) and added sodium chloride (10 Gm. daily) had been instituted. At this time the patients had been discharged from the hospital and were living in rural districts where constant medical supervision was not possible. Patient 15 was known to have had evidence of preexisting myocardial damage which antedated treatment with desoxycorticosterone acetate. Patient 11 did not have signs of circulatory failure until her blood pressure had reached a hypertensive level (175 systolic, 95 diastolic). It is possible that this patient may have had preexisting vascular disease, although this cannot be stated with certainty. There is no doubt, however, that the striking increase in plasma volume, blood pressure, body weight and activity which followed continued treatment in both cases was a major factor in precipitating the myocardial failure.

Withdrawal of sodium chloride from the diet, restriction of fluids, absolute bed rest and digitalization fortunately resulted in marked improvement in both cases. It is quite possible that these vascular accidents and some of those reported by other investigators [13] might have been avoided if the patients could have been followed more carefully after discharge from the hospital.

The striking and continued improvement which has been observed in the majority of patients treated for

*Treated with Desoxycorticosterone Acetate*

| Present Therapy | | Present Status | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Desoxycorticosterone Acetate | Added Sodium Chloride | Hematocrit Volume of Packed Cells, % | Serum Sodium, mEq./L. | Serum Potassium, mEq./L. | Serum Chloride, mEq./L. | Serum $CO_2$ Combining Power, mEq./L. | Blood Nonprotein Nitrogen, Mg./100 Cc. | Blood Sugar, Mg./100 Cc. | Total Protein Serum, Gm./100 Cc. | Condition | Occupation | Activity |
| Pellets (16) | 5 Gm. | 40.1 | 138.0 | 5.6 | 100.4 | 24.6 | 27 | 87 | 6.5 | Good | Clergyman | ++++ |
| Pellets (7) | 10 Gm. | 33.6 | 143.7 | 4.7 | 111.2 | 24.3 | 22 | 84 | 5.6 | Good | Housewife | +++ |
| Pellets (16) | None | 38.1 | 137.7 | 4.6 | 104.0 | 23.3 | 28 | 84 | 5.5 | Good | Shopkeeper | ++++ |
| Pellets (5) | None | 41.3 | 137.7 | 4.5 | 105.6 | 24.6 | 34 | 77 | 5.3 | Good | Housewife | ++++ |
| Pellets (13) | None | 35.8 | 138.8 | 5.0 | 105.2 | 24.6 | 31 | 71 | 5.9 | Good | Manual laborer | ++++ |
| Pellets (13) | 8 Gm. | 38.3 | 144.0 | 3.5 | 95.2 | 32.4 | 23 | 81 | 6.4 | Good | Unemployed | ++++ |
| Pellets (8) | 10 Gm. | 37.5 | 145.4 | 6.1 | 106.2 | 28.4 | 26 | 80 | 5.3 | Fair | Unemployed | +++ |
| Pellets (9) | None | 41.9 | 141.9 | 4.7 | 99.0 | 31.6 | 30 | 85 | 5.4 | Good | Office worker | ++++ |
| Pellets (4) | None | 40.1 | 145.4 | 4.3 | 107.6 | 21.7 | 28 | 95 | 5.2 | Good | Office worker | ++++ |
| Pellets (7) | None | 39.6 | 139.4 | 4.7 | 103.6 | 24.3 | 27 | 74 | 5.7 | Good | Office worker | ++++ |
| Pellets (14) | None | 40.7 | 134.3 | 3.1 | 100.0 | 23.8 | 32 | 87 | 7.6 | Poor | Housewife | ++ |
| ..... | ..... | .... | ..... | ... | ..... | .... | .. | .. | ... | Died (discontinued therapy) | | |
| Pellets (8) | None | 39.0 | 143.4 | 5.4 | 103.6 | 24.3 | 34 | 91 | 6.4 | Good | Housewife | +++ |
| Pellets (9) | 4 Gm. | 41.1 | 135.3 | 5.9 | 107.2 | 23.8 | 28 | 76 | 5.7 | Good | Unemployed | +++ |
| Pellets (10) | None | 35.2 | 138.9 | 4.7 | 103.8 | 27.1 | 25 | 69 | 5.9 | Fair | Housewife | ++ |
| Pellets (5) | None | 44.0 | 138.7 | 4.3 | 105.8 | 26.8 | 30 | 76 | 6.1 | Good | Farm chores | +++ |
| Pellets (6) | None | 32.8 | 143.5 | 4.2 | 103.6 | 25.8 | 24 | 80 | 5.6 | Fair | Housewife | +++ |
| Pellets (8) | None | 40.0 | 142.6 | 3.8 | 107.6 | 27.1 | 23 | 90 | 6.0 | Good | Housewife | ++++ |
| Pellets (8) | None | 39.7 | 139.3 | 3.6 | 114.2 | 30.0 | 28 | 88 | 5.6 | Good | Office worker | ++++ |
| Pellets (2) | None | 41.6 | 144.2 | 5.2 | 103.4 | 31.8 | 30 | 80 | 6.0 | Fair | Shopkeeper | +++ |
| Pellets (4) | 8 Gm. | 38.0 | 143.4 | 4.7 | 104.8 | 24.6 | 28 | 75 | 5.5 | Good | Unemployed | ++++ |
| Pellets (5) | None | 40.1 | 138.8 | 4.9 | 100.2 | 24.3 | 28 | 90 | 5.3 | Poor | Hospital patient | + |
| ..... | ..... | .... | ..... | ... | ..... | .... | .. | .. | ... | Died (intercurrent infection) | | |
| Pellets (5) | 2 Gm. | 37.7 | 137.6 | 5.0 | 107.6 | 22.9 | 24 | 78 | 5.7 | Good | Stenographer | ++++ |
| Daily injection, 2.5 mg. | 4 Gm. | .... | ..... | ... | ..... | .... | .. | .. | ... | Good | Stenographer | ++++ |
| Pellets (4) | None | 31.3 | 137.3 | 4.6 | 108.4 | 25.0 | 26 | 75 | 5.8 | Good | Unemployed | +++ |
| Pellets (8) | 5 Gm. | 33.7 | 139.8 | 5.3 | 102.6 | 25.4 | 25 | 85 | 5.7 | Poor | Housewife | ++ |
| Daily injection, 2.5 mg. | 6 Gm. | .... | ..... | ... | ..... | .... | .. | .. | ... | Good | Housewife | ++++ |
| Pellets (10) | 2 Gm. | 49.8 | 144.6 | 4.5 | 105.2 | 27.9 | 26 | 86 | 5.4 | Good | Unemployed | +++ |
| Daily injection, 1.5 mg. | None | .... | ..... | ... | ..... | .... | .. | .. | ... | Good | Garageman | ++++ |

13. Wilder, R. M., and Rynearson, E. H.: Personal communication to the authors. Ferrebee, Ragan, Atchley and Loeb.[4]

periods as long as from six to eighteen months with the synthetic adrenal principle strongly suggests that some abnormal disturbance must have existed in the cardiovascular system of those patients in whom signs and symptoms of circulatory failure developed during treatment. Several possibilities are apparent: (*a*) preexisting myocardial, valvular or vascular disease unrelated to Addison's disease; (*b*) permanent myocardial or vascular disease resulting from a long-continued state of adrenal insufficiency; (*c*) hypoglycemia; (*d*) alteration in electrolyte concentration, i. e. high sodium and low potassium levels, and (*e*) a specific metabolic disturbance in cardiac muscle associated with adrenal insufficiency not corrected by desoxycorticosterone acetate treatment. Certainly the grave nature of these possible complications indicates the need for great care in instituting treatment with the synthetic adrenal factor.

### INTERCURRENT INFECTIONS

The effectiveness of desoxycorticosterone acetate treatment in supporting patients with Addison's disease during the course of intercurrent infections and throughout operations deserves special note. The clinical condition of patient 6 was so much improved after this treatment that a nephrectomy was performed because of extensive active tuberculous infection of one kidney. At present, approximately one year after operation, the patient is in excellent condition. It is believed that this represents the first reported case in which a nephrectomy [14] has been successfully performed on a patient with far advanced Addison's disease. Patient 16 was sustained during a series of acute infections which consisted of a streptococcic throat infection associated with erythema nodosum and complicated later by pneumonia. Patient 23 was maintained in relatively good condition for a period of several weeks following postoperative complications of pneumonia and pelvic phlebitis, although she succumbed ultimately to a colon bacillus septicemia. Several patients have had infections of the upper respiratory tract from which they have recovered rather promptly in contrast to delayed recovery from attacks previous to treatment. Patient 7 sufficiently improved with the synthetic adrenal factor to permit the removal of a tuberculous epididymis. At present, eighteen months after desoxycorticosterone acetate treatment was instituted, a tuberculous sinus tract has healed completely, his right wrist joint, which was the site of an active tuberculous infection, is greatly improved and his general condition is remarkably good.

TABLE 4.—*Summary of Treatment with Synthetic Adrenal Cortical Factor*

| | |
|---|---|
| Number of patients | 30 (males 16, females 14) |
| Days of treatment | 247 (mean) 50-444 (range) |
| Blood pressure | |
| Before treatment | 98/67 mm. of Hg (mean) |
| At present | 134/89 mm. of Hg (mean) |
| Body weight | |
| Before treatment | 54.2 Kg. (mean) |
| At present | 58.8 Kg. (mean) |
| Present condition of patients | |
| Good | 21 |
| Fair | 4 |
| Poor | 3 |
| Died during treatment | 1 |
| Died after treatment discontinued | 1 |
| Total | 30 |

### CARBOHYDRATE METABOLISM

Prior to the substitution of the synthetic adrenal principle a majority of the patients in this study were found to have a flat type of dextrose tolerance (oral) curve as well as a marked predisposition to develop hypoglycemia three or four hours after receiving dextrose either orally or intravenously. It is significant that not all untreated patients with typical Addison's syndrome showed these changes.

The mean value for fasting blood sugar for all the patients before treatment was 80 mg. per hundred cubic centimeters (Folin-Wu method). Treatment with desoxycorticosterone acetate did not significantly affect the fasting blood sugar level. In nearly all the cases long-continued treatment (from six to eighteen months) with the synthetic compound was followed by a tendency for the dextrose tolerance (oral) curve to return to normal values with some amelioration of the hypoglycemia which had been observed to occur after the administration of dextrose. In contrast to the rapid restoration (in from one to three weeks) of serum electrolyte concentration and the somewhat slower (from four to eight weeks) but complete restoration of blood pressure to the normal level, changes in carbohydrate metabolism occurred much more slowly (after six to eighteen months of continued treatment) and were much less complete.

It is possible that the improvement in carbohydrate metabolism which was noted may have been merely an accompaniment of the great improvement in the clinical condition of the patients and not necessarily the result of a specific effect of desoxycorticosterone acetate on carbohydrate metabolism. Further studies are necessary before this question can be answered.

### PIGMENTATION

Continued treatment (from six to fifteen months) with the synthetic adrenal cortical factor has been followed by an appreciable decrease in pigmentation in twelve of the cases reported in this study. To date, however, complete disappearance of abnormal pigmentation has not been observed in any instance.

### COMMENT

Desoxycorticosterone is one of several crystalline compounds which have been isolated from adrenal cortical extracts. It is by no means certain that any one of the compounds thus far isolated represents the active form of the naturally occurring hormone. As tested by its potency in maintaining the life of adrenalectomized animals, desoxycorticosterone is the most active of all the compounds thus far identified. Other compounds less active in life-maintaining effect have been shown to possess marked activity in other respects. Long, Katzin and Fry [15] and Jensen and Grattan [16] have shown the marked glycotropic effect of corticosterone and dehydrocorticosterone, and Ingle [17] has demonstrated the effectiveness of these two compounds in maintaining muscular activity. It is also possible that some of the

14. The successful nephrectomy was performed by Dr. Lloyd Lewis, associate in the Department of Urology, Johns Hopkins University and Hospital.

15. Long, C. N. H.; Katzin, B., and Fry, Edith G.: The Adrenal Cortex and Carbohydrate Metabolism, Endocrinology **26**: 309 (Feb.) 1940.

16. Jensen, H., and Grattan, J. F.: The Identity of the Glycotropic (Anti-Insulin) Substance of the Anterior Pituitary Gland, Am. J. Physiol. **128**: 270 (Jan.) 1940.

17. Ingle, D. J.: The Work Performance of Adrenalectomized Rats Treated with Corticosterone and Chemically Related Components, abstr., Am. J. Physiol. **126**: 543 (July) 1939.

so-called "inactive" compounds may also possess activity when appropriate tests are devised. To date desoxycorticosterone is the only compound which has been synthesized and the only crystalline compound which can be obtained in quantities sufficient for clinical trial.

Thus far the use of desoxycorticosterone acetate has been restricted to the treatment of patients with classic signs and symptoms of Addison's disease. This therapy is indicated if patients with Addison's disease are unable to resume normal activity when treated with adequate quantities of sodium chloride and a diet low in potassium. The demonstration that the administration of excessive doses of the adrenal cortical factor to normal animals resulted in adrenal cortical atrophy scarcely justifies withholding specific desoxycorticosterone therapy from patients with Addison's disease.

It is evident that the quantity of supplementary sodium chloride administered to such patients must be carefully regulated during treatment with desoxycorticosterone acetate. Excessive quantities of the synthetic adrenal cortical principle and sodium chloride may result in the appearance of edema, hypertension and, in some instances, signs of congestive heart failure. Occasionally the appearance of edema or an excessive rise in blood pressure may necessitate a reduction in the dose of desoxycorticosterone acetate before the maximum therapeutic effect has been attained. Since the great increase in blood volume, the rise in blood pressure and the increased physical activity which follow the institution of treatment with the synthetic compound rather suddenly place a considerable additional load on the cardiovascular system, it is advisable to restore most patients rather slowly to normal activity. The grave nature of these possible complications indicates the need for care in the institution of treatment and the necessity for continued medical supervision.

It has been noted that in a majority of patients with Addison's disease hypoglycemia readily develops three or four hours after either oral or intravenous administration of dextrose.[18] An appreciation of this fact is necessary if serious complications are to be avoided after the administration of dextrose solutions to patients in adrenal crisis. The delayed and incomplete effect of desoxycorticosterone acetate therapy in correcting this disturbance in carbohydrate metabolism is in marked contrast to the prompt and striking effect on electrolyte metabolism and blood pressure.

The greatest single obstacle to the successful treatment of adrenal cortical insufficiency is the difficulty with which the diagnosis is established early in the course of the disease. Several diagnostic procedures have been suggested.[19] All of these have some disadvantage or limitation. It is possible that treatment with a minimal effective dose of crystalline hormone for a limited period may be of aid in diagnosis. However, it is by no means certain that a favorable response to such therapy is necessarily specific.

## SUMMARY AND CONCLUSIONS

Treatment with the synthetic adrenal cortical principle (desoxycorticosterone acetate) appears to be an efficacious form of specific therapy for patients with Addison's disease. The uniform potency and stability of the crystalline product permit more exact regulation of therapy. The relative inexpensiveness of treatment with desoxycorticosterone acetate will permit most patients to afford adequate therapy.

Striking and continued clinical improvement was observed in twenty-one of thirty cases reported in this study. Clinical improvement was associated with a retention of sodium, chloride and water, an increased renal excretion of potassium, a marked increase in plasma volume, restoration of the concentration of sodium, chloride and potassium of the plasma to normal values, an increase in body weight and an increase in both systolic and diastolic blood pressures. Complete rehabilitation of the patients did not occur until the disorder in electrolyte metabolism had been corrected and the blood pressure restored to a normal level. However, clinical improvement did not always parallel restoration of the plasma concentration of electrolytes and the return of blood pressure to a normal level.

The effect of desoxycorticosterone acetate therapy in restoring carbohydrate metabolism to normal was neither as prompt nor as complete as the effect in correcting the disorder in electrolyte metabolism and in raising the blood pressure. The predisposition of patients with Addison's disease to have marked hypoglycemia following the oral or parenteral administration of dextrose solutions indicates the need for extreme care in the use of these solutions in the treatment of adrenal crisis.

The great increase in blood volume, the rise in blood pressure and the increased physical activity which follow the institution of desoxycorticosterone acetate therapy place a considerable additional load rather suddenly on the cardiovascular system. For this reason it is recommended that the activity of patients be restricted during the first few weeks of treatment.

It is apparent that the quantity of supplementary sodium chloride must be regulated carefully throughout the period of desoxycorticosterone acetate treatment. The use of excessive doses of the synthetic compound and added sodium chloride may result in the appearance of edema, hypertension and signs of congestive heart failure. The incidence of these untoward reactions may be greatly reduced if reasonable care is exercised in the regulation of the dosage of the adrenal cortical factor and added sodium chloride.

Pellets of crystalline desoxycorticosterone acetate, implanted subcutaneously, may be substituted successfully for daily intramuscular injections of the drug in oil. The implantation of pellets not only obviates the necessity for daily oil injections but also provides a more constant supply of the material and results in a considerable saving (from 30 to 40 per cent) in the quantity required. A single implantation of pellets (each weighing approximately 125 mg.) should supply continuous and adequate therapy for a period of nine to twelve months. The number of pellets which are needed may be calculated accurately from the daily dose of desoxycorticosterone acetate in oil required to maintain the patient in good condition. One pellet (125 mg.) is required for each 0.4 to 0.5 mg. of the compound in oil. Implantation of pellets should not be considered until a patient has been maintained in good condition for a period of from six to eight weeks by means of a daily injection of desoxycorticosterone acetate in oil and until the daily quantity of the substance necessary for satisfactory maintenance has been determined accurately.

18. Thorn, G. W.; Koepf, G. F.; Kuhlmann, D., and Olsen, E. F.: A Study of Carbohydrate Metabolism in Experimental Adrenal Insufficiency and in Patients with Addison's Disease, Effect of Desoxycorticosterone Acetate Treatment; abstr., Am. J. Physiol., to be published.

19. Thorn, G. W.: Adrenal Cortical Hormone Therapy, Am. J. M. Sc. **197**: 718 (May) 1939.