Long-Term Management of Patients After Adrenalectomy

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Since the initial reports of Huggins et al. in 1952 on the favorable palliative effect of surgical adrenalectomy on the course of some patients with metastatic carcinoma of the breast, there have been a number of papers by other groups of investigators reporting similar observations. I have been a participant in a team from the Cedars of Lebanon Hospital in Los Angeles which some two years ago reported their results of palliative treatment of metastatic breast carcinoma by surgical adrenalectomy. The essential conclusion of that report was that surgical adrenalectomy was a palliative procedure suitable for selected patients with metastatic cancer of the breast. Since adrenalectomy induces a second disease in patients already seriously ill, it would seem that a prime consideration in the selection of this procedure as a therapeutic choice offered to patients with metastatic breast disease, would be the ease or difficulty of the long-term management of patients after removal of the glands. Surprisingly, there is scant information in the literature on this very point. The present report is a review of experience in the long-term medical management of 17 patients previously subjected to surgical adrenalectomy.

Description of Patients

Sixteen patients, all women, had metastatic carcinoma of the breast, and adrenalectomy was performed as a therapeutic palliative procedure in the management of the disease. One patient, a male, had a large cyst of an adrenal gland, and severe adrenal insufficiency developed after surgical removal of the adrenal cyst with the adrenal gland attached. Six patients were observed for one year or longer, the longest period being almost three years. Another four patients were observed for from six to twelve months before death from cancer supervened; and the remaining patients died of cancer within six months after operation. The patient with the adrenal cyst is alive and well six months after operation.

Maintenance Adrenal Cortical Replacement Requirements

The criteria by which long-term adrenal replacement therapy were considered adequate were as follows: (1) Sense of well-being; (2) avoidance of symptoms of adrenal insufficiency (weakness, anorexia, nausea, vomiting, fever, hypotension, tachycardia); (3) absence of orthostatic hypotension; (4) normal serum electrolyte concentrations. The best indicator of adequate replacement therapy was the patient's subjective sense of well-being. If the patient complained of weakness or fatigue in the absence of active metastatic disease, it was considered a sign for adjustment of the replacement medication. It is worth stressing that no laboratory test was as valuable as the patients' subjective response.

The basic adrenal cortical factors necessary to fulfill the foregoing criteria are steroids active in maintaining salt and water balance (mineralocorticoid activity), and steroids potent in glucocorticoid (hydrocortisone-like) activity. Since no single known adrenal cortical steroid compound is capable of adequately supplying the above factors without unwanted side effects at any dose level, we employed a combination of the following substances as re-
placement therapy: (1) Cortisone, (2) desoxycorticosterone acetate (DOCA), and (3) sodium chloride.

1. Cortisone. All 17 patients received cortisone by mouth in divided doses at a total daily dose level of 37.5 to 50 mg. Attempts to lower the daily dose to 25 mg. in several patients resulted in loss of well-being and the onset of symptoms of weakness, fatigue and anorexia. Doses exceeding 50 mg. daily ultimately caused edema and rounding of the face.

2. Desoxycorticosterone. All 17 patients in this series were given DOCA, 2 mg. daily, sublingually. The use of a long-acting parenteral repository form of DOCA (Desoxycorticosterone trimethylacetate) was tried in a few patients, but this route of administration was discarded for the following reasons: (a) Uncertainty as to the exact time when another injection was needed, and (b) the development of edema if larger doses of cortisone were required for any reason.

3. Sodium chloride. All patients were permitted ad libitum use of salt in their diets. Seven patients in this series required supplemental doses of sodium chloride tablets, 1 to 4 grams daily, in order to maintain normal serum electrolyte concentrations.

It is a matter of interest, that under stable conditions (that is, in the absence of infection, injury or surgical treatment), established dosage schedules required surprisingly little adjustment over long periods. In warm weather, some patients required extra supplements of salt and a slightly higher daily dose of cortisone (for example, 50 mg. instead of 37.5 mg.). In general, minimal maintenance requirements were needed during the cooler winter weather. In the six patients observed for a year or longer, the only variations in maintenance medication consisted in adjustments of the cortisone dosage between 37.5 and 50 mg., and in the need for extra sodium chloride supplements. In all instances, the dosage of DOCA was kept constant at 2 mg. daily.

There are slight variations from our regimen in the published adrenal cortical replacement programs of other investigators. Huggins and Dao suggested the implantation of DOCA pellets, rather than the use of the oral form of this compound. The University of California group also expressed preference for parenteral administration of DOCA. They suggested intramuscular injections of desoxycorticosterone trimethylacetate every 21 to 30 days. Pearson also expressed the opinion that cortisone only, in an oral daily dose of 50 to 75 mg., along with liberal salting of the diet. Very recently, Leith and Beck suggested the combined use of 9-alpha-fluorohydrocortisone and hydrocortisone in the management of chronic adrenal insufficiency. I have had no experience with this regimen.

The following case report illustrates the need for the combination of mineralocorticoid and glucocorticoid steroid activity plus an adequate salt intake in the replacement program of a patient after adrenalectomy.

CASE 1. A 60-year-old white woman was admitted to the hospital, seven months after bilateral oophorectomy and adrenalectomy, for the purpose of adjusting her adrenal cortical replacement regimen. Surgical adrenalectomy had been performed because of the appearance of pulmonary metastases. Following operation, there was no further progression of metastatic disease. The patient felt well, gained weight and had excellent appetite. However, she complained of angina of effort. The blood pressure was within normal limits. Several electrocardiograms were interpreted as normal. One Master exercise test was interpreted as normal and another test was called positive for coronary insufficiency. X-ray films of the chest showed the heart to be normal in size. However, the patient was found to have pronounced hypercholesterolemia. Two serum cholesterol determinations were done and the content was 555 and 630 mg. per 100 cc. The basal metabolism rate was +17 per cent. Protein-bound iodine and thyroid radioactive iodine uptake studies could not be performed because of a recent gallbladder x-ray study.

Adrenal cortical replacement medication consisted of cortisone, 50 mg. daily by mouth and DOCA, 2 mg. sublingually daily. Diet was unrestricted as to sodium content. Dietary salt restriction, as an outpatient, had resulted in lessening of the anginal symptoms, but the patient would become weak and tired. Accordingly, she was admitted to the hospital for closer observation and study.

The pertinent observations during the stay in hospital are shown in Chart 1, and may be summarized as follows:

1. Serum electrolytes were normal during the first three days in hospital, medication remaining the same as the patient had received as an outpatient.

2. During the next 15 days, Meticorten® in doses of 10 to 15 mg. daily was given in place of cortisone and DOCA. A diet unrestricted in sodium was continued. During the first eight days, 1 to 3 gram daily supplements of sodium chloride were given, and during the last seven days DOCA, 2 mg. daily, was also given. The body weight decreased 7 pounds, the serum sodium concentration dropped below the normal range, and the serum potassium concentration exceeded the upper limits of normal. These changes are consistent with inadequate mineralocorticoid and/or salt replacement. Clinically, angina disappeared, but the patient became weak and listless, and anorexia and nausea developed.

3. During the next 12 days, the original regimen of cortisone, 50 mg. daily, and DOCA, 2 mg. daily, was resumed, with reversal of the changes noted
above. Body weight increased 4 pounds and serum electrolytes returned to normal concentrations. Anorexia, weakness and nausea disappeared, but angina returned.

4. During the next 15-day period, the administration of cortisone and DOCA was continued without change in dosage, but limitation of low sodium intake to 400 mg. daily was instituted. Again, the patient lost weight and anorexia, weakness and nausea developed. Serum sodium concentration dropped and serum potassium rose. Angina again subsided. Again, the patient showed evidence of mineralocorticoid and salt insufficiency.

MANAGEMENT OF PATIENTS SUBJECTED TO STRESS

It has long been recognized clinically that patients with spontaneous Addison's disease could quickly be thrown into adrenal crisis following the introduction of a bodily stress such as surgical operation, trauma or infection. Recent studies have shown that blood 17-hydroxycorticosteroid levels increase following stresses such as surgical operation. This is believed due in part to the increased adrenal secretion of these steroids. These observations are particularly pertinent to the patient whose adrenal glands have been removed. It would mean that the adrenal cortical replacement requirements of such patients should be temporarily raised whenever they are subjected to a significant stress. The commonest stresses encountered by the group of patients here reported upon were infections, particularly upper respiratory tract infections. Patients who have had adrenalectomy should be constantly instructed on the necessity of consulting their physician at the first sign of an infection of any sort. Moreover, they should be repeatedly taught a basic method of increasing their cortisone intake should they be caught in an emergency situation, such as an accident or the inability to reach their physician immediately.

Management of Mild Infections

The incidence of mild infections, such as the usually epidemic diseases of the upper respiratory tract, did not appear to be any higher in the present group of patients who had had adrenalectomy than would ordinarily be expected in the rest of the population. These patients had an average of from none to two...
of the common viral and respiratory tract infections a year. Properly controlled patients who have had adrenalectomy are not more susceptible to infections, but the consequences of infection may be more severe in them.

The usual adjustment routine in the present series was to increase the dose of cortisone to 100 mg. daily orally (25 mg. four times a day) for two days, then to lower the dose to 75 mg. daily in divided doses for two days, and then finally to return to 50 mg. daily. Usually no change was made in the dose of DOCA and the intake of sodium chloride. Antibiotics by mouth were usually recommended, even in circumstances in which these substances would not be advised for ordinary patients, in order to minimize the chances of development of severe, overwhelming infection. Parenteral glucocorticoids were only advised when the patient could not retain oral medication because of vomiting. In many cases of minor infections sufficient advice could be given over the telephone, but the patient was in contact with the physician once or twice daily during the course of the illness. If the physician had the slightest doubt as to the status of the patient, the patient was seen at home or at the office, depending upon the particular circumstances at hand.

Management of Severe Infections

In three patients in this series acute adrenal insufficiency was precipitated by a serious infection characterized by severe systemic reactions. One patient had an acute bronchiolitis and died in adrenal insufficiency, the only death in this group of patients attributable to the absence of adrenal glands. A second patient had acute tonsillitis with lymphadenitis, and the third patient had a urinary tract infection with pronounced systemic manifestations. It might be well to remark here that three very characteristic signs of impending adrenal crisis are: (1) Intense weakness, (2) intense restlessness and apprehension, and (3) generalized migratory and often severe skeletal pain. Often the patient is unable to state precisely where the pain is, but that intense pain is being endured is a certainty. These symptoms are excellent indicators for immediate admittance to hospital, close observation and intensive therapy.

The basic guiding principles for the management of acute adrenal insufficiency with impending or acute adrenal crisis are:

1. The primary need is for more glucocorticoids.
2. The parenteral route of administration of steroids is important.
3. The physician should know the optimal time of action of the various glucocorticoid preparations.
4. The patient should not be overloaded with fluids and salt.

5. The intensive administration of antibiotics if infection is present or suspected.

I. The primary need is more glucocorticoids

Mendelsohn and Pearson induced profound clinical collapse in six patients who had had adrenalectomy by withdrawing their daily cortisone medication. They found that changes in salt and water metabolism were not of great magnitude and develop slowly. They concluded that the vigorous administration of glucocorticoids was the crux of treatment of adrenal crisis in these patients. My clinical experience is in agreement with these observations. The primary requirement is for more cortisone or hydrocortisone, not for more DOCA and salt.

As a matter of fact, the latter are not necessary, in my experience, whenever the daily dose of cortisone exceeds 100 mg.

II. Parenteral route of administration of glucocorticoids

I firmly believe that an acutely ill patient who has had adrenalectomy should always receive glucocorticoids parenterally. I prefer the intramuscular administration of cortisone for basic long range control and the intravenous infusion of hydrocortisone for the acute immediate emergency. Dependence on cortisone by mouth at any dose level is deemed hazardous in dealing with an acutely ill patient because of uncertainty as to absorption of the medication, the frequent presence of nausea and vomiting, the lack of certainty that the patient will take the drug regularly and the clinically erratic effect of oral medication in these patients.

III. Time of action of glucocorticoid preparations

An absolute requirement for successful preventive or therapeutic management of acute adrenal cortical insufficiency is a thorough familiarity of the optimal time of action and route of administration of the various adrenalcortical preparations. There are short acting and long acting compounds; there are quickly acting and delayed acting dosage forms; there are drugs best suited for immediate emergency situations, and drugs better suited for longer range maintenance effects. The situation is analogous to the problem of selecting the proper digitalis preparation. Unfortunately, many physicians are not aware of the basic characteristics of the various steroid preparations. As with digitalis, it is best to become conversant with the use of two or three preparations, preferably a quick acting drug for emergency use and a longer acting preparation for long range control. The following is a thumbnail sketch of the salient features of the important available glucocorticoid compounds.
1. Cortisone

(a) Oral. The oral tablets are eminently suitable for long term ambulatory therapy under stable conditions. The absorption of cortisone is more rapid after oral administration than after intramuscular administration. The clinical effect of cortisone taken by mouth is manifest within four hours and may persist for from eight to twelve hours.\textsuperscript{17} Although quicker in onset of action, the duration of action is shorter than following intramuscular administration. As already stated, I do not feel that the oral route of administration is dependable in the acutely ill adrenalectomized patient.

(b) Intramuscular. Cortisone acetate given intramuscularly requires about 12 hours to begin to exert an appreciable clinical effect. A maximum effect is achieved in about 24 to 48 hours.\textsuperscript{15,17} In my opinion, intramuscular cortisone provides the best basic parenteral glucocorticoid preparation for treatment over a period of several days. It provides a steady dependable therapeutic "floor" in an acutely ill patient. Similarly, its effects persist for 48 to 96 hours after administration of it is discontinued. However, it is not suitable for emergency use since it does not exert a significant action in time.

2. Intravenous hydrocortisone

The intravenous preparations of hydrocortisone are the preparations best suited for emergency situations. A significant clinical response may be achieved within one hour after the intravenous administration of 100 mg. hydrocortisone.\textsuperscript{14} Significant sodium retention begins within two hours.\textsuperscript{7} There are two forms of hydrocortisone commercially available for intravenous use:

(a) Free hydrocortisone in 50 per cent alcohol (packaged in dose of 100 mg. in a 20 cc. ampul). This must be diluted in 500 to 1000 cc. of distilled water or saline solution and given by constant drip.

(b) Hydrocortisone hemisuccinate, a water-soluble form of hydrocortisone, in which form 100 mg. can be given by direct intravenous injection in a 2 cc. volume of fluid.\textsuperscript{11}

3. Other compounds

I have not employed prednisone and prednisolone in the treatment of acute adrenal insufficiency because of their negligible mineralocorticoid activity as compared to cortisone and hydrocortisone. Fluorohydrocortisone, on the other hand, would exert too great a mineralocorticoid effect in the doses necessary to combat acute adrenal insufficiency. An older intravenous preparation useful in emergency is aqueous adrenal cortical extract administered repeatedly in sufficient dosage.

IV. Parenteral fluids

It has been my practice to follow current principles of postoperative fluid administration.\textsuperscript{10} Generally, not more than 2000 ml. of fluid per 24 hours is administered. I prefer to use glucose in distilled water rather than in saline solution. Moderate decreases in serum sodium and chloride concentrations were not considered matters of great concern, provided the patient's clinical condition was satisfactory. If sodium chloride was deemed necessary, not more than 1 liter of half-normal sodium chloride solution was given intravenously per day. In general, I preferred letting the patient obtain the salt he needed by mouth, usually when he began to eat. It is worth re-emphasizing that cortisone and hydrocortisone in daily doses exceeding 100 mg. have a significant sodium-retaining or mineralocorticoid effect.\textsuperscript{17} This is also the reason for my belief that the administration of DOCA is not necessary when large doses of cortisone or hydrocortisone are employed.

General Therapeutic Scheme for Patients with Acute Adrenal Insufficiency

This is fundamentally the same as outlined in a previous paper\textsuperscript{13} for the operative and postoperative management of patients undergoing adrenalectomy. Briefly, the following routine is suggested:

1. Immediate intravenous injection of 100 mg. hydrocortisone hemisuccinate.

2. Follow with slow intravenous drip of 100 mg. hydrocortisone contained in 500 ml. of 5 per cent glucose in distilled water.

3. Concurrently, give 150 mg. of cortisone acetate intramuscularly and subsequently give 50 mg. intramuscularly every four hours around the clock. Thus, a total of 300 to 400 mg. cortisone is given intramuscularly during the first 24 hours.

4. Further intravenous infusions of hydrocortisone during the first 24 hours depend upon clinical response of patient.

5. On succeeding days, gradually reduce the total daily dose of intramuscular cortisone acetate given in spaced multiple injections—for example, 200 mg. on the second day, 150 mg. the third day and 100 mg. the fourth day.

6. Occasionally, the concurrent parenteral use of vasoconstrictors such as norepinephrine is necessary if the patient is in shock and does not respond in a reasonable time.

It is to be remembered that other physicians employ other satisfactory routines, such as the use of intravenous hydrocortisone alone, or the intramuscular use of hydrocortisone hemisuccinate.\textsuperscript{2,3,14}

The following case report illustrates some of the principles just discussed:

Case 2. The patient was a 36-year-old white woman who had had bilateral oophorectomy and adrenalectomy six weeks before for palliation of
advanced carcinoma of the breast with metastasis to the brain, chest wall and bones. Maintenance medication consisted of cortisone, 50 mg. daily by mouth and sublingual DOCA, 2 mg. daily. Four days before the present admittance to hospital she became weak, anorexic and complained of generalized aching of the body. Accordingly, the dose of cortisone by mouth was increased to 100 mg. a day. Despite this, she became progressively weaker, very restless and complained of severe generalized pains involving the head, left axilla, both flank areas over the sites of incision and the lower abdomen. On the morning of admission to the hospital the temperature rose to 101°F., and she was nauseated. Upon admission to the hospital in the afternoon, she was started on cortisone 30 mg. intramuscularly every eight hours and procaine penicillin 600,000 units intramuscularly every twelve hours. The next morning, there was a temperature spike to 105°F. and the patient went into adrenal collapse. She was bathed in a cold sweat, was intermittently cyanotic, had a thready pulse at a rate of 140 to 160 beats per minute, had Cheyne-Stokes respiration, and appeared lethargic and semicomatose. Upon physical examination an intensely reddened pharynx and follicular tonsillitis were noted. The left posterior auricular and posterior cervical lymph nodes were decidedly enlarged, hot and exquisitely tender. Leukocytes numbered 6,800 per cu. mm. of blood—79 per cent polymorphonuclear cells with 45 per cent stabs.

Emergency measures consisted of the administration of 100 mg. of hydrocortisone contained in 1000 ml. of 5 per cent glucose in distilled water by constant intravenous drip, cortisone by intramuscular injection, 50 mg. every four hours, and large parenteral doses of penicillin and terramycin. During the first 24 hours of therapy, the patient received a total of 200 mg. of hydrocortisone intravenously, 300 mg. of cortisone intramuscularly and 2,000 ml. of 5 per cent glucose in water intravenously. Within 24 hours, there was a decided clinical improvement and the temperature was normal and remained so. The patient recovered and left the hospital in ten days.

This case illustrates the following points:

1. The precipitation of acute adrenal collapse by a severe infection with pronounced systemic manifestations—in this case, acute tonsillitis with accompanying acute lymphadenitis.

2. Typical premonitory symptoms of impending adrenal crisis; that is, intense weakness, apprehension and severe generalized pains.

3. The failure of the oral administration of cortisone to forestall the collapse, despite a doubling of the maintenance dose.

4. Failure to appreciate the significance of the premonitory symptoms of adrenal crisis in time to take adequate measures to prevent collapse; that is, the administration of parenteral glucocorticoids and large doses of antibiotics.

5. The failure to appreciate the lag period in cortisone action after beginning intramuscular administration upon admission of the patient to the hospital. This contributed to the development of adrenal collapse.

6. Finally, the dramatic response to the emergency use of intravenous hydrocortisone supplemented by large doses of intramuscular cortisone.

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REFERENCES


