THE USE OF CORTISONE IN THE TREATMENT OF THE PANHYPOPITUITARISM DUE TO POSTPARTUM NECROSIS OF THE PITUITARY (SHEEHAN'S SYNDROME)

E. PERRY McCULLAGH, M.D., PENN G. SKILLERN, M.D.
Department of Endocrinology

and

CARL A. SCHAFFENBURG, M.D.
Research Division

IN a series of articles, the first of which was published in 1914, Simmonds[1-3] described destruction of the anterior lobe of the pituitary gland and its clinical effects. This condition became known as Simmonds' disease.

Knowledge of this disease has been greatly broadened by the work of Sheehan,[4,5] who, in 1937, first described areas of pituitary infarction and fibrosis due to thrombosis with necrosis occurring in women having a history of severe postpartum hemorrhage accompanied by shock and usually coma. The anterior pituitary failure which results from this type of lesion is usually, but not always, more extensive than that produced by other types of lesions of the pituitary. If the gonadotropins, thyrotropin and corticotropin are all absent, the condition is termed "panhypopituitarism," despite the fact that the function of the posterior lobe is not known to be unimpaired. If the secretion of only one or two of these hormones is deficient, the condition may be termed "selective" or "partial" pituitary failure.

Thus, the symptoms and signs of the panhypopituitarism of Sheehan's syndrome are largely due to the effects of secondary atrophy and failure of the adrenal cortices, the thyroid and the ovaries. Most of these symptoms, signs and laboratory findings are described in the following two case studies.

The main purpose of this paper is to discuss the use of cortisone or hydrocortisone in the treatment of the adrenal cortical failure that occurs secondary to severe anterior pituitary failure.

CASE REPORTS

Case 1. A 33 year old white woman was first seen here in October 1937. Six years prior to admission she had had a severe postpartum hemorrhage with shock requiring packing of the uterus during an otherwise normal delivery. This was her first pregnancy. She was unable to nurse her baby and developed permanent amenorrhea. Her energy and endurance decreased and she lost 10 pounds in weight during the next two years.

Her skin became dry and her axillary and pubic hair became scanty. There was no appreciable change in sexual libido.

Physical examination revealed her height to be 63 inches, and weight 115 pounds. Her blood pressure was 100/70 mm. Hg. The skin was dry. The pubic hair was sparse and the axillary hair was almost absent. There was some loss of hair from the eyebrows. The external genitalia were normal. The uterus was atrophic and the vaginal wall was devoid of rugae. There was no excessive pigmentation of the skin.

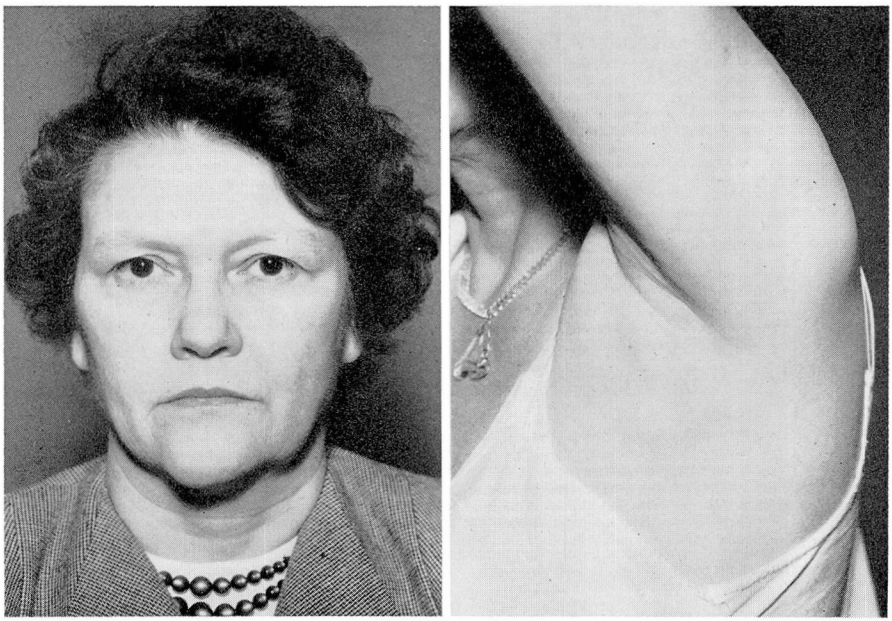
Laboratory examination revealed the following: X-ray of the sella turcica was normal. The basal metabolic rate was minus 20 per cent. Urinalysis was negative. The red blood cell count was 4,340,000, the hemoglobin was 78 per cent, and the white blood cell count was 5650. The blood sugar was 92 mg. per 100 cc. 3¾ hours post cibum.

A diagnosis of anterior pituitary deficiency was made.

Therapy with 1½ gr. desiccated thyroid per day and 200 U. APL three times weekly was initiated. However, although the patient felt some initial improvement, response could not be accurately evaluated because she discontinued the medication and contact with her was lost.

Fourteen years later in October 1951, the patient was readmitted with the same complaints; sexual libido had now disappeared.

Physical findings were substantially the same as on her previous visit. Her weight was 124 pounds and the blood pressure was 108/74. Photographs of the patient taken at this time are shown in figure 1.



(a) (b)

Fig. 1. (Case 1) Sheehan's syndrome with mild adrenal cortical failure. (a) Facies essentially normal except for pallor. (b) Left axilla demonstrating loss of axillary hair.

The serum sodium and serum potassium levels were 133 and 4.8 mEq/L., respectively. The plasma cholesterol was 328 mg. per 100 cc. Fasting blood sugar was 97 mg. per 100 cc., and a single dose, oral, glucose tolerance test showed the following: fasting 97 mg., one-half hour 126 mg., one hour 122 mg., two hours 119 mg., three hours 77 mg., and four hours 111 mg. per 100 cc. The basal metabolic rate was minus 24 per cent. Adrenalin and ACTH tests revealed a fall of 35 and 54 per cent, respectively, of eosinophils in the blood at the end of four hours. Original counts were 72 and 156, respectively. Urinary gonadotropins were more than 6 but less than 13 m.u. per 24 hours. The urinary 17-ketosteroids were 0.7 mg. per 24 hours. The vaginal smear was castrate in type and the uterus was atrophic. The uterine canal was 5 cm. in length. The endometrium was so atrophic that no material could be obtained for biopsy.

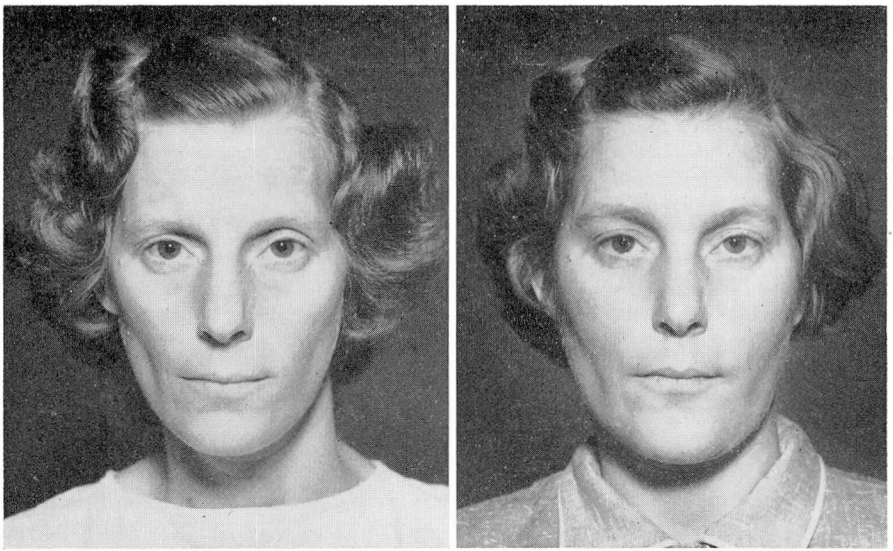
The patient was started on oral cortisone, 50 mg. per day divided into four doses, and she was advised to return in four weeks to receive desiccated thyroid and testosterone. Although her condition improved at the beginning of cortisone treatment, she soon experienced a sense of nervous stimulation and irritability that caused her to discontinue the therapy. She described herself as being "all keyed-up" while taking the drugs, and did not return for the thyroid and androgen treatment. When she returned one and a half years later, an I^{131} test revealed an uptake of 10 per cent in 24 hours. The plasma cholesterol was 387 mg. per 100 cc. The basal metabolic rate was minus 34 per cent. A dose of 12.5 mg. a day of cortisone was prescribed and the patient noted marked improvement in strength and appetite. Her skin was still dry and pale, and her nails were somewhat brittle. Blood pressure was 110/82. Therapy with cortisone was continued and she was given 1 gr. of U.S.P. desiccated thyroid daily. Three months later, her plasma cholesterol was 232 mg. per 100 cc. Ten mg. of testosterone (buccal) was administered twice a day. On her return three months later, she reported that she felt entirely normal for the first time in 20 years. Her sexual libido had returned to normal. There was some light hair on the chin and cheeks. Her weight was 135 pounds. The blood pressure was 130/82; the plasma cholesterol was 226 mg. per 100 cc.; and the basal metabolic rate remained low, being minus 27 per cent.

Case 2. A 33 year old white woman was first examined here on August 4, 1953. She was chiefly concerned in regard to extreme weakness, oligomenorrhea, a weight loss of 18 pounds and episodes of coma.

Her history revealed that in 1943, after her second child was delivered, she had a severe uterine hemorrhage followed by profound shock. She recovered with the aid of blood transfusions without any residual effects, except that during the next three years she noted weakness and a loss of weight from 140 to 120 pounds. Her menstrual periods continued to be regular; they had always been scanty and lasted three days. In 1945, she had her third child. Two days after arriving home, the patient again had a uterine hemorrhage, but in this instance it was not followed by shock.

In 1951, six years after the birth of her third child, the patient first noted the onset of oligomenorrhea; during this year she had only four menses, in 1952 she had two, and in 1953 she had two scanty menses for three days each in April and August.

In June 1951 during an episode of migraine headache associated with vomiting, the patient lapsed into a coma which lasted three days from which she recovered spontaneously. In May 1953 during another episode of migraine associated with vomiting, the patient again lapsed into coma for two days. Two blood samples obtained during this episode were found to have blood sugar contents of 16 and 32 mg. per 100 cc., respectively. The patient was promptly revived by only the intravenous administration of glucose. Three weeks prior to her initial examination here a third episode of hypoglycemic coma relieved by glucose occurred which again followed migraine headache



(a) (b)

Fig. 2. (Case 2) Sheehan's syndrome with severe adrenal cortical failure. (a) Typical facies demonstrating apathy, pallor and weight loss prior to treatment. (b) Essentially normal facies following three months of treatment with cortisone, desiccated thyroid and estrogen.

associated with vomiting. She had experienced neither nausea nor vomiting during the time between the episodes of hypoglycemic coma. Because of a poor appetite her weight had decreased 18 pounds during the two years preceding the examination. Her weakness had become so extreme that she was unable to do any of her housework.

Treatment of the patient's condition had consisted of 1 gr. of desiccated thyroid taken daily for the two years prior to admission and injections of ACTH three times a week for a few weeks prior to admission. No estrogen had been prescribed.

Physical examination revealed her weight to be 102 pounds and her height to be 62 inches. The systolic blood pressure was 90 mm. Hg, but diastolic pressure could not be recorded in the sitting position. The patient was apathetic, pale and listless. Axillary hair was absent and pubic hair was scant. Pelvic examination disclosed no evidence of a pathologic condition or genital atrophy. There was some melanosis over the forehead and sides of the face which the patient said had been present for the past year. She had noticed the same condition during each pregnancy but it had disappeared after each delivery. There was no increased pigmentation elsewhere on her body.

Laboratory studies revealed a flat glucose tolerance curve with hypoglycemia. The blood sugar levels were as follows: fasting 62 mg., one hour 77 mg., two hours 50 mg., three hours 48 mg., and four hours 42 mg. per 100 cc. No insulin tolerance test was done in view of the obvious hypoglycemia. The first part of the Robinson-Kepler-Power test showed an overnight urine volume of 645 cc., and the largest hourly volume after ingestion of 20 cc. of water per Kg. of body weight was 35 cc. The Kepler index was 0.4. The ACTH test was normal with a 60 per cent fall in eosinophils from 200 to 81. Blood studies revealed the sodium to be 129 mEq., potassium 3.8 mEq., carbon dioxide 26.1 mEq., and chlorides 99 mEq. per liter; the serum calcium was 10.5 mg., phosphorus

3.5 mg., and cholesterol 205 mg. per 100 cc. A differential white blood cell count showed 41 per cent neutrophils, 7 per cent eosinophils, and 52 per cent lymphocytes. The basal metabolic rate was minus 38 per cent. The 24-hour urinary 17-ketosteroid value was .2 mg. (normal, 5 to 9 mg.). There were no corticoids found in a 24-hour urine specimen (method of Reddy, Jenkins and Thorn[6]). The hemoglobin content was 13.4 Gm. X-ray of the sella turcica was normal. Microscopic examination of two specimens of urine, including one catheterized specimen, revealed marked pyuria. A vaginal smear was loaded with pus and trichomonads.

Treatment consisted of the simultaneous administration of 50 mg. of cortisone, 1 gr. of U.S.P. desiccated thyroid every day and 1 mg. of stilbesterol daily for 25 of each 30 days. Small doses of testosterone or methyltestosterone may be added to the therapy program in the future if necessary. While the patient was taking cortisone, the blood sugar levels before each meal were 62 mg., 64 mg., and 111 mg. per 100 cc. The patient was not given feedings between meals, She was advised to use salt liberally but not excessively in her food.

On November 7, 1953, the patient returned saying that she felt completely well for the first time since 1943. She was more alert, her appetite was good, and she had gained 18 pounds in weight. She was able to do all of her housework with ease. Her sexual libido had returned. The hypoglycemic attacks had not recurred. Her axillary hair was beginning to return. There was no edema of the legs. On her face, the pallor had disappeared and the melanosis (chloasma) had almost completely disappeared. Figure 2 includes photographs of the patient before and after therapy.

Laboratory study at this time showed a basal metabolic rate of minus 20 per cent, fasting blood sugar of 80 mg. per 100 cc., plasma cholesterol of 235 mg. per 100 cc., and a differential white blood cell count of 61 per cent neutrophils, 2 per cent eosinophils, and 37 per cent lymphocytes.

DISCUSSION

These two patients with panhypopituitarism presented quantitive and qualitative differences in the manifestations of their disease. While the first patient developed amenorrhea following the onset of pituitary failure and never menstruated again, the second patient continued to menstruate regularly every month for eight years after the episode of necrosis of the pituitary gland. Oligomenorrhea occurred in the second patient two years before admission, but the menses, though rare, did not cease. Also, she was capable of becoming pregnant two years after the first episode of postpartum hemorrhage, indicating that, although pituitary failure already existed as evidenced by the presence of weakness and weight loss, ovarian function was still adequate. This is not an uncommon occurrence in this type of pituitary failure. Sheehan[5] states that permanent amenorrhea occurs in the most severe cases only, while in the less severe cases the menses may persist for a few months to several years and then stop. In others the menses may return completely to normal.

There were no characteristic physical findings that indicated that either one of these patients was truly myxedematous, i.e., swollen puffy face and delayed reflexes, but there were changes that suggested that they might have mild hypothyroidism.

The adrenal cortical failure in case 2 was much more marked than that in case 1, as evidenced by the second patient's (case 2) apathy, severe weakness, extreme weight loss and episodes of hypoglycemic coma relieved by the intravenous administration of glucose. This type of hypoglycemic coma without electrolytic changes should be distinguished from acute adrenal cortical failure or adrenal crisis which is usually evidenced by electrolyte changes with or without hypoglycemia. The former may be relieved by intravenous glucose alone, while the latter will require, in addition, replacement adrenal cortical therapy. The organic hypoglycemic episodes in the second patient were precipitated by migraine headaches associated with vomiting; the headache and vomiting caused an inadequate intake of food which resulted in a blood sugar content so low that coma occurred. The intravenous administration of glucose alone promptly revived her from her comatose state. The hypoglycemia in the second patient may be due both to a deficiency of growth hormone that has an anti-insulin effect and to a deficiency of ACTH that helps to maintain the blood sugar level by stimulating the adrenal cortices.

In treating adrenal cortical failure, the physician must decide whether to use physiologic stimulative therapy with ACTH, or replacement therapy with cortisone (Compound E) or hydrocortisone (Compound F). Cook, Bean, Franklin and Embrick,[7] Schrock, Sheets and Bean,[8] and Summers and Sheehan[9] have noted that patients with this syndrome respond much more satisfactorily to cortisone than they do to ACTH. Knowlton, Jailer, Hamilton and West[10] also have noted a poor response to ACTH in their patients. These authors[7-10] believe that the presence of long-standing adrenal cortical atrophy is the reason for the unsatisfactory response to ACTH. Furthermore, Summers and Sheehan[9] noted the occurrence of hemiparesis in two patients who received 25 mg. of ACTH every eight hours. The paresis disappeared after treatment was discontinued. Schrock, Sheets and Bean[8] noted the development of toxic psychosis in their patient treated with 25 mg. of ACTH every six hours. It is likely that doses of ACTH, not excessive under other circumstances, may have been excessive in these cases[7-10] and were responsible for the striking untoward symptoms. Heyde[11] noted that his patient with Sheehan's syndrome, who responded rapidly to ACTH, developed insomnia on 15 mg. of ACTH a day which disappeared when the same dose was given every other day. In contrast to the previous reports, he noted that 10 mg. of corticotropin gel every third day and 2.5 mg. of desoxycorticosterone every day plus other glandular replacement therapy were sufficient to maintain the patient in good health. Maddock, Leach, Klein and Myers[12] noted that the administration of 10 to 20 mg. of ACTH every six hours produced a good response in four men with selective pituitary failure and marked secondary adrenal cortical failure. However, this response did not occur until the third day of administration. In addition, they noted that 25 mg. of ACTH a day maintained these patients satisfactorily.

Therefore, while the adrenal cortex in some patients with panhypopituitarism may respond to ACTH, the experience quoted has shown that consist-

ently good results cannot be predicted. In addition, those who do respond may have a delayed response which is also a disadvantage particularly if one has to treat a patient in adrenal crisis. Thus, it is our belief that cortisone or hydrocortisone is to be preferred instead of ACTH. That cortisone may produce a rapid as well as effective response is substantiated by Abbott and Simmons[13] who reported that their patient with Sheehan's syndrome in adrenal crisis responded in 24 hours to 200 mg. of cortisone. For continuous therapy it is particularly advantageous that cortisone is active when administered orally.

It is important that the dose of cortisone be individualized. The first patient (case 1) felt so stimulated and uncomfortable that she was unwilling to continue taking 50 mg. of cortisone daily which was originally prescribed. When the dose was reduced to 12.5 mg. per day she noted a great symptomatic improvement and the disappearance of the stimulation. On the other hand, the second patient (case 2) did well on 50 mg. of cortisone a day and experienced no toxic symptoms. The rather marked hypoglycemia was corrected by this dosage. Skillern and Rynearson[14] and Steiner[15] have also noted that cortisone is most beneficial in controlling the hypoglycemia of pituitary failure. It should be stressed to the patient that if she is unable to take cortisone by mouth due to illness, she should inform her doctor immediately so that he can give her the needed cortisone intramuscularly. The dose should be increased for the duration of the illness.

Cortisone seems to be beneficial not only to patients with clinical adrenal cortical failure such as that which is present in Sheehan's syndrome, but also in the type of adrenal deficiency which may occur secondary to other types of pituitary lesions. However, we would like to emphasize that many patients, especially men, with certain types of pituitary failure, such as that seen postoperatively or in the presence of sellar, suprasellar or parasellar, space-taking lesions of various sorts, may be improved greatly by testosterone alone. In fact, some, who have not only severe gonadal deficiency but readily measurable evidence of adrenal defect as well, may evidence so much improvement on testosterone alone that the addition of cortisone scarcely seems to be needed. In some patients we have observed that the addition of cortisone causes little or no further symptomatic response and is not worth continuing.[16] However, if patients such as these are subjected to any severe stress it may be wise to use cortisone.

Hydrocortisone may be used instead of cortisone. The properties of this drug have been reviewed recently by Thorn and his associates.[17] The metabolic effects of hydrocortisone are qualitatively similar to those of cortisone. The main difference is that hydrocortisone is about twice as potent as cortisone milligram for milligram; therefore, the dose of hydrocortisone should be about one half of the estimated dose of cortisone. The only disadvantage of hydrocortisone is that it is ineffective when administered intramuscularly, being effective only when it is given orally. This drug is now available and offers one advantage over cortisone in that it is less likely to produce central nervous system stimulation to which these patients and those with Addison's disease

seem peculiarly susceptible, sometimes even when small average maintenance doses are given.

We believe that a regular diet without frequent feeding is sufficient in these patients. We advise the patient to use salt liberally on his food, but we do not prescribe any extra salt. If the patient requires less than 50 mg. of cortisone a day it may be necessary to prescribe 2 to 4 mg. of desoxycorticosterone (linguets) a day, if the blood pressure remains low, symptoms of weakness persist and electrolytes in the blood remain low after a few weeks of treatment.

Since no good anterior pituitary extract is readily available, other replacement hormone therapy is also necessary in severe cases such as the two we have presented. If an adequate dose of cortisone is prescribed, there is no reason why 1 gr. of uncoated U.S.P. desiccated thyroid cannot be started simultaneously since the danger of precipitating adrenal crisis has been eliminated. Schrock, Sheets and Bean[8] noted that a patient with Sheehan's disease developed obvious myxedema when given cortisone alone which was corrected by adding desiccated thyroid. These same authors[8] noted that in the presence of adrenal cortical deficiency the administration of desiccated thyroid precipitated adrenal crisis when cortisone was withheld. Means, Hertz and Lerman[18] and Perkins and Rynearson[19] have emphasized the danger of giving desiccated thyroid alone to patients having severe pituitary failure such as usually is seen in Sheehan's syndrome.

In the premenopausal woman (before the age of 45 years) it is also advisable to recommend estrogen replacement therapy, such as stilbesterol 1 mg. a day 25 of each 30 days. Since the normal androgens are almost totally missing from the body, it is logical that some androgen be given. For this, methyltestosterone may be administered as sublingual tablets in a dose of 10 mg. or more per day. This will help to maintain a normal protein balance, will restore normal sexual libido, and will assist in the normal regrowth of axillary and pubic hair.

The transformation of the condition of such patients as these from that of chronic invalidism before treatment to one of essentially normal health following therapy is most striking and gratifying. There is no doubt in our minds that cortisone was chiefly responsible for the improvement in the two patients whose case reports we have presented here.

SUMMARY

The clinical features and laboratory findings in two cases of panhypopituitarism due to postpartum necrosis of the pituitary gland have been presented. Multiple glandular replacement therapy, particularly cortisone, transformed the state of these women from one of chronic ill health to one of essentially normal health. In our second patient, cortisone not only relieved the systemic effects of adrenal insufficiency but also corrected a severe hypoglycemia. The use of cortisone or hydrocortisone in preference to ACTH is advocated because they are more surely effective, more rapidly effective, and more easily administered.

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