RESULTS OF THE ADMINISTRATION OF ACTH TO A PATIENT SUFFERING FROM SHEEHAN'S SYNDROME

BY

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In 1914 Simmonds described a syndrome which has been called after him. The name: hypophyseal cachexia indicates that extreme progressive emaciation is the chief symptom, while a feeling of weakness and weariness and a loss of strength and energy are accompanying symptoms.

A premature ageing and an atrophy of the skin and of the internal organs, particularly of the sexual organs is observed. There is a loss of pubic and axillary hair and eyelashes while the hair on the head becomes thin.

Pathological-anatomical examination has revealed that the cause of the syndrome is a complete or partial degeneration of the hypophysis, especially of the anterior lobe due to tumours, inflammations (lues, tuberculosis, nonspecific inflammations following infectious diseases or embolisms).

Sheehan, in a number of brilliant articles (1937, 1938, 1939) has shown that the most important cause of Simmonds' disease is necrosis of the anterior lobe of the hypophysis resulting from postpartum collapse, which may or may not be accompanied by a severe hemorrhage. It is practically only in these obstetrical conditions that the anterior lobe of the hypo-
physic is selectively injured. The symptoms which occur result from cessation of the functions of this organ.

Only in a very small number of cases suffering from Simmonds' disease could the above mentioned cause be confirmed. There are usually other symptoms in addition to those already mentioned. All these symptoms are the result of the destruction of the total hypophysis and there is also injury to the surrounding tissues.

For the rest it is a matter of opinion whether the disease is called »Simmonds' disease« due to post-partum necrosis of the anterior pituitary as Sheehan himself does, or »Sheehan's disease (or syndrome)«. Our opinion is that the latter name is to be preferred, not only because of the fact that if a name is to be linked up with this disease it should be Sheehan's, but also because the syndrome has a definite pathological anatomical basis, a clear distinct aetiology and forms a comprehensive pathophysiological whole, which is not always the case with the cachexia of Simmonds. Moreover Sheehan has pointed out that cachexia is not a prominent symptom in the syndrome described by him.

Sheehan's disease was discovered as a result of a pathological-anatomical and clinical study. Endocrinological investigations in a narrower sense have hardly been performed by him. It should be of value to investigate an advanced case of this disease as closely as possible. If this is done, it will become clear that, however critical Sheehan's studies may have been, there are a few cases among those described by him, in which the diagnosis must be considered doubtful. The clinical diagnosis may not be accepted if it is not based also on endocrinological investigations. The investigations may give us an insight into the course of the disease which does not always present quite the same clinical picture. Sheehan has already observed that the extent of the necrosis varies and that the deficiency phenomena vary both in intensity and in nature.

While the syndrome described by Sheehan has a partial necrosis of the anterior lobe of the hypophysis, caused by ischemia, as its pathological anatomical basis, the clinical
phenomena may be explained by assuming a cessation of a number of hypophyseal functions: gonadotrophic (amenorrhea) thyrotrophic (low B.M.R.) and corticotrophic (low excretion in 17-ketosteroids and 11-oxysteroids).

The discontinuation of the factor stimulating the adrenal glands is ultimately the most striking phenomenon (and eventually the cause of death). We have investigated the effect of ACTH on a patient suffering from Sheehan’s syndrome. We were led to make this investigation by certain considerations. It is not unusual for patients suffering from Addison’s disease to have an amenorrhea for which it is not so easy to account. Albright reports a case of Addison’s disease in which no gonadotrophic substances were excreted. Thorn and his co-workers reported a uterine hemorrhage, 6—10 days after one injection of 25 mg. of ACTH, in 3 of their patients, who had not menstruated for more than a year and among whom was 1 case of Addison’s disease. Hence it seemed possible that the amenorrhea in Sheehan’s syndrome resulted from insufficiency of the adrenal glands or in other words from a gonadotropic insufficiency secondary to the corticotrophic insufficiency. Should this be the case, certain therapeutic possibilities occur, such as not treating the patients with gonadotrophic preparations or steroidal sex hormones. In order to test this possibility we examined the influence of treatment with ACTH on the F.S.H. content of the urine of a patient suffering from Sheehan’s syndrome. In addition we examined some functions of the adrenal glands and gonads.

**CASE RECORD**

On July 7th 1949 a 48-year old woman came to our endocrinological policlinic with the clinical diagnosis: »Sheehan’s syndrome«. The history was a typical one. After the 12th and last partus (9 years ago) she had become less and less fit. The delivery was complicated by a manual removal of the placenta. The loss of blood after the birth of the child had been so considerable that the patient had collapsed. Lactation after the partus was absent in contrast to all the other parturitions when the patient had been able to nurse the child for 6—7 months. Post partum an amenorrhea had persisted and
from this she had never recovered. She became cold, listless and rather thin. She was easily fatigued and looked very pale. There was a considerable loss of hair from the head which only partly grew again later on. Her muscular strength had decreased. During the last few years the patient had suffered from itching and she had been hospitalized for this in our department of dermatology on July 4th 1949. On July 21th she had been transferred for observation to the department of gynecology.

The examination revealed a woman who looked much older than her age. Her physical condition was tolerable good. The skin was very pale and the mucous membranes were rather rich in blood. The patient was compos mentis. Her speech was very slow and her voice was low. There was no axillary hair at all and the pubic hair was practically absent. The eyebrows had fallen out on the lateral side. The hair on the head was rather thin. The mammae were atrophic. Her weight was 66 kg. She was 157 cm. in height; her span was 162 cm. Her bloodpressure was 110—75: pulse was regular. The thyroid gland was not palpable. Her heart and lungs did not show any abnormalities. Many old striae were seen on the abdomen. The skin was dry and atrophic. To give a idea of what the patient looked like before and after the last partus, we have given 2 photographs. (cf. Fig. 1).

![Fig. 1. Photograph of the patient before and after she got ill.](image)

The roentgenogram of sella and spinal column did not show any abnormalities.

The external genitalia were normal. Internal examination revealed a very small uterus in anteflexion and no palpable adnexa. The total length of the uterus was 6 cm.
Laboratory findings only confirmed the clinical diagnosis. The results were as follows: F. S. H. tested on 4 U: negative; total quantity of 17-ketosteroids 2.6 mg. per 24 hrs. (ab. 11 mg. is normal), the excretion of 11-oxysteroids was 0.3 mg. per 24 hrs. (ab. 1 mg. is normal). The basal metabolism on July 4th was plus 13 per cent. It should be noted that the patient had been taking pulv. gland. thyr. at home for two years up to the day of hospitalization. After she had been admitted to hospital no more thyroideum was administered, which resulted in a decrease of the basal metabolism, first to —6 per cent and then to —33 per cent (16—9—'49).

The bloodpicture was as follows: hemoglobin content 72—90 normal). Erythrocytes 4.000.000, leukocytes 5.500. Differential count: eosinophils 2, basophils 0, stabforms 1, segmented forms 51, lymphocytes 42, monocytes 4. Erythrocytes in section 7.7. Sedimentation rate was 5 and 11 mm. after 1 and 2 hrs. resp. Biopsy of the endometrium showed that there was no mucous membrane in the uterus. A vaginal smear revealed that there were no oestrogenic substances.

The excretion of 17-ketosteroids, 11-oxysteroids and gonadotrophins in the urine of our patient strongly suggested that both the corticotrophic and gonadotrophic activities of the hypophysis had ceased. The metabolism, which was —33 per cent two months after the thyroid therapy suggested a less active, thyrotrophic factor.

The patient who, from a clinical point of view too, showed the classical Sheehan's syndrome, was injected on 6 consecutive days with a daily quantity of 25 mg. of corticotrophin. We investigated whether this treatment, had any effect on:

1. the F.S.H. content of the urine,
2. the blood picture,
3. the electrolytes in the blood,
4. the excretion of 17-ketosteroids,
5. the excretion of 11-oxysteroids,
6. the insulin tolerance test,
7. the ratio uric acid-creatinine excretion,
8. the bloodsugar values in the fasting patient,
9. the bloodpressure,
10. the diuresis.

In the literature we found the following data on the effect of ACTH in normal and diseased subjects. Forsham et al. (1948) have described some detailed observations, made after the injection of ACTH. They come to the conclusion that one single dose of 25 mg., injected intramuscularly, is usually very
well tolerated. Sometimes secondary phenomena are observed such as bradycardia, slight colica and in the case of women, uterine cramps. Some patients grew pale immediately after the injections, but usually these phenomena disappear within 45 minutes. These are attributed to presence of a low content of posterior lobe hormones in the preparation used. After the injection of one single dose (the so-called Thorn test) marked, hematological changes occurred. The maximal effect was observed within 4 hrs. after the injection. This effect is characterized by a sudden decrease in the circulating eosinophil leukocytes, together with a less marked decrease in lymphocytes and an increase in neutrophil granulocytes which is possibly not quite specific. In most patients with normal adrenal glands the circulating eosinophils decreased by 74 per cent. Patients suffering from Addison’s disease had a decrease of only 4 per cent.

One single injection of 25 mg. of ACTH was followed by an increased excretion of sodium, chlorine, potassium and uric acid. The creatinine excretion remained constant or was decreased. Here too a maximal effect was observed within 4 hrs. after the injection. The increase in the ratio uric acid-creatinine is about 85 per cent in normal subjects (with normal adrenal glands) while in patients suffering from Addison’s disease there is only an average increase of 16 per cent. Thorn has described a functional test for the adrenal glands, based on these two differences in normal subjects and in patients suffering from Addison’s disease. This was based on the assumption that the changes seen in normal subjects depended on a good functional activity of the adrenal cortex. Forsham et al. also recorded hematological and metabolic changes in normal subjects, to whom ACTH had been administered for 4—6 days under standardized conditions.

These observations suggest that all the known functions of the adrenal cortex seem to be affected. In the first place we observe an increased excretion of 17-ketosteroids and secondly an increased excretion of corticosteroids. Not only do we find an increase in the 11-oxysteroid content of the urine, but an
increased excretion is also suggested by an increase in the blood sugar values in the fasting subject, possibly as a result of an increased gluconeogenesis.

An increased excretion of desoxycorticosterone-like substances is suggested by the sodium and chlorine retention in cases with increased potassium excretion. When ACTH was no longer administered, sodium and chlorine were excreted in greater quantities.


This was determined by the ultrafiltration method as described by Gorbman using a colloid membrane with constant properties. When the urine is passed through it, the albuminous hormones remain on the filter. The filtrate is then injected into infantile female mice and the increase in weight of the uteri is determined by means of a torsion balance.

The current conception of the aetiology of amenorrhea in cases of Sheehan's syndrome is that all functions of the hypophysis, gonadotrophic included, are primarily involved. The reasons for doubting this view were:

a. A patient suffering from Addison's disease may also have an amenorrhea, while the most striking changes in Sheehan's syndrome are essentially due to an insufficiency of the adrenal glands.

b. Forsham et al. (1948) have demonstrated that ACTH causes hemorrhage in women with amenorrhea.

c. Sheehan in his survey of 1939 writes: »there are sometimes related menopausal symptoms, such as flushing of the face, for a year or two, but these are inconstant«. In these cases it seems as if the ovarian function ceases before the gonadotrophic function of the hypophysis.

Starting from a primarily or secondarily disturbed function of the adrenal glands, an amenorrhea may theoretically arise in one of the following ways:

1. The adrenal gland no longer supplies any precursors or if it does, it is no longer sufficient, so that an ovarian amenorrhea results.
2. As a result of the general depression, the adrenal gland deficiency results in an insufficient production of gonadotrophic hormone by the hypophysis. A low F.S.H. excretion is then to be expected.

Our patient was 48 years old. Normally she would have reached the climacteric. If the discontinuation of the gonadotrophic function is secondary to that of the corticotrophic function recovery of the gonadotrophic function with ACTH treatment is to be expected.

While our patient was being injected with 25 mg. of ACTH from July 27th to August 1st included, the gonadotrophic determinations were as follows:

July 14th: F. S. H. tested with 4 U: negative.
July 29th: F. S. H. tested with 4 U: negative.
July 31th: F. S. H. tested with 4 U: negative.
August 3rd: F. S. H. tested with 4 U: negative.
August 5th: F. S. H. tested with 4 U: negative.
August 8th—9th: F. S. H. tested with 2½ U: negative.
August 10th: F. S. H. tested with 4 U: negative.

These results are not in disagreement with the view that the gonadotrophic function of the hypophysis is also primarily destroyed. The effect obtained by Thorn, who observed a uterine hemorrhage 6—10 days after one injection of 25 mg. of ACTH in 3 patients who had not menstruated for more than a year cannot be explained unless it is assumed that ACTH stimulated the oestrogenic function of the adrenal cortex.

In our patient we did not find any increase in oestrogenic substances after the treatment (the quantity of oestrogenic substances before and after the treatment was less than 40 U, probably 0).

Pompen (1945) showed that an increased oestrogenic function may occur under the influence of ACTH treatment in a patient suffering from Sheehan's syndrome. Whether the oestrogenic function in this case resulted from certain frac-
tions of the 17-ketosteroids is perhaps worthy of consideration.

Thus our results do not support that the gonadotrophic hypophyseal function in cases of Sheehan's syndrome is disturbed of a primary discontinuation of the corticotrophic function. It is quite possible however that in our case the test was of too short a duration.

2. Hematological changes.

With regard to the blood picture Sheehan has reported that the number of leukocytes was normal or a little below normal (4000—6500), in a case of the syndrome which he described as »Simmonds' disease« due to postpartum necrosis of the anterior lobe of the hypophysis. Quite often there was a relative lymphocytosis. In 16 cases he found an average of 2300 lymphocytes, and 3400 polynuclear leukocytes. In one third of the cases the number of eosinophils was below 2 per cent, in one third of the cases 3—6 per cent and in the remainder of the cases 7—12 per cent. Hence a relatively large number of eosinophils is quite normal in these cases. With regard to the red blood picture, Sheehan reports a slight anemia. During the first five years of this syndrome, he found 5—6 million erythrocytes and a low colour index, viz. 0.6—0.8. In the next 10 years the number of erythrocytes is 3—4 million and the colour index is higher, viz. 0.7—0.9. In our patient, who had been suffering from this disease for 8 years, the haemoglobin content was 72, the number of erythrocytes 4 million, the colour index 0.9.

With ACTH treatment we did not observe any considerable changes in the number of neutrophil leukocytes in our patient. The eosinophil leukocytes, counted according to Dunger did not decrease below 50 per cent of the original number. Thorn has emphasised that this value is required to establish adrenal glands with normal functions. Taking the mean of the three determinations before the first ACTH injection and comparing it with the decrease after the first injection, we find a decrease of 36 per cent. This is considerably more than is generally
found in patients suffering from Addison's disease (Thorn gives an average of 4 per cent) but considerably less than in normal subjects where the decrease is on an average 74 per cent.

The number of lymphocytes increases and decreases practically in the same proportion as do the total number of leukocytes, but always remains on a high level (cf. Fig. 2).

![Graph showing hematologic changes](image)

**Fig. 2.**

Changes in the number of leukocytes and lymphocytes after the treatment with ACTH.

With regard to the hematological changes observed in the experiment involving injections of 25 mg. of ACTH daily during a period of 4—6 days (which most closely resembles our
treatment), Thorn believes that these changes are similar to those observed after one single injection. Thus in the case of normal subjects he finds the marked decrease to a low level in the circulating eosinophils, which has already been mentioned. This decrease continues as long as ACTH is administered. When ACTH is no longer administered there is an immediate return to normal values. With regard to neutrophil granulocytes we may say that an increase to a high level is always found, while decrease is observed when ACTH is no longer administered. The lymphocytes usually show a decrease followed by an increase to values above the original level.

In addition to normal subjects and patients suffering from Addison's disease, Thorn examined a number of patients with hypophyseal insufficiency among whom were 3 cases of Simmonds' disease. It appeared that the greatest number of patients with insufficiency of the anterior lobe of the hypophysis showed little or no response to ACTH. The changes in the number of circulating eosinophils and the changes in the ratio uric acid-creatinine in his cases of Simmonds' disease were:

<table>
<thead>
<tr>
<th>Simmonds' disease, 42 years old (severe case)</th>
<th>Changes in circulating eos.</th>
<th>Changes uric acid-creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+ 24 per cent</td>
<td>+ 1 per cent</td>
</tr>
<tr>
<td>Simmonds' disease, 33 years old (severe case)</td>
<td>- 4 » »</td>
<td>+ 18 » »</td>
</tr>
<tr>
<td>Simmonds' disease, 61 years old (moderate)</td>
<td>- 17 » »</td>
<td>+ 22 » »</td>
</tr>
<tr>
<td>Our patient (Sheehan's syndrome)</td>
<td>- 36 » »</td>
<td>+ 68 » »</td>
</tr>
</tbody>
</table>

3. Changes of electrolytes in the blood.

Before ACTH was administered to our patient, the sodium, potassium and chlorine content of the blood was determined twice and the chlorine percentage of the plasma and of the erythrocytes once. The hematocrit values were also determined.
The values found before, during and after the treatment were as follows:

<table>
<thead>
<tr>
<th>Date</th>
<th>Sodium</th>
<th>Potassium</th>
<th>Chlorine (plasma)</th>
<th>Chlorine (blood)</th>
<th>Chlorine (erythrocytes)</th>
<th>Hematocrit values</th>
</tr>
</thead>
<tbody>
<tr>
<td>July</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26th</td>
<td>338</td>
<td>27.2</td>
<td>585</td>
<td>522</td>
<td>368</td>
<td>29</td>
</tr>
<tr>
<td>27th</td>
<td>358</td>
<td>45.4</td>
<td>—</td>
<td>497</td>
<td>—</td>
<td>33</td>
</tr>
<tr>
<td>30th</td>
<td>—</td>
<td>—</td>
<td>582</td>
<td>540</td>
<td>473</td>
<td>37</td>
</tr>
<tr>
<td>August</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5th</td>
<td>320</td>
<td>18.2</td>
<td>594</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>9th</td>
<td>372</td>
<td>20.8</td>
<td>597</td>
<td>519</td>
<td>345</td>
<td>31</td>
</tr>
</tbody>
</table>

These figures have been graphically represented in Fig. 3. The difficulty in obtaining determinations makes us hesitate to draw any definite conclusions. If any can be drawn they suggest a decreased «desoxycorticosterone» function of the adrenal glands.

Fig. 3.

Values of Sodium, Potassium, Chlorine (plasma), Chlorine (blood), Chlorine (erythrocytes), during treatment with ACTH.

As well as Forsham, Thorn, Prunty & Hills (1948), Mason et al. (1948) have made a detailed investigation on the effect of ACTH, especially on the excretion of steroids in the urine. The increase in excretion of steroids in normal subjects under the influence of ACTH is considered by them to be due to a stimulation of the adrenal cortex. The daily excretion of 17-ketosteroids and corticosteroids was found to be three times higher, while the occurrence of acne in a normal woman suggested that the production of androgenic substances was also increased. Mason in his case found an increase in the 17-ketosteroid excretion from 4.84 to 15.5 mg. per 24 hrs. During the period of ACTH administration the quantity of androsterone and aetiocholanolone excreted was definitely increased.

The values of the excretion of 17-ketosteroids in our patient are given in Fig. 4.

![Excretion of 17-ketosteroids and 11-oxysteroids during treatment with ACTH.](image)

**Fig. 4.** Excretion of 17-ketosteroids and 11-oxysteroids during treatment with ACTH.
The normal values, obtained by the method of determination used, vary from 5—19 mg. per 24 hrs. with an average value of 11 mg. Thus we generally obtained very low values, while an increased excretion after ACTH administration was rarely observed. The total absence of 17-ketosteroids in the urine on August 3rd suggests a complete exhaustion of the adrenal glands.

5. Changes in the excretion of 11-oxysteroids in the urine.

Mason et al. (1948) described an increase in the excretion of corticosteroids in the urine of a normal young woman from 0.18 to 1.44 mg. per 24 hrs. after 100 mg. of ACTH had been administered.

The method of Heard & Sobel (1946) was used for this determination. In normal subjects we found an excretion of 0.8—1.2 mg. per 24 hrs.

The following values were found in our patient:

<table>
<thead>
<tr>
<th>July</th>
<th>24th: 0.32 mg. per 24 hrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>» 26th: 0.45 » » » »</td>
<td></td>
</tr>
<tr>
<td>» 28th: 0.50 » » » »</td>
<td></td>
</tr>
<tr>
<td>» 30th: 0.76 » » » »</td>
<td></td>
</tr>
<tr>
<td>August</td>
<td>1th: 0.57 » » » »</td>
</tr>
<tr>
<td>» 3rd: 0.57 » » » »</td>
<td></td>
</tr>
<tr>
<td>» 30th: 0.54 » » » »</td>
<td></td>
</tr>
</tbody>
</table>

The various values are given in Fig. 4. It appears that the 11-oxysteroids show a slight response to ACTH treatment.

6. The insulin tolerance test.

From investigations performed by Mason et al. (1948) it appeared that the insulin resistance was increased under the influence of ACTH. Before treatment our patient no insulin tolerance test was performed in order to avoid the possibility of affecting other values. On August 4th. i.e. 3 days after the last injection, it was found that the bloodsugar values, after the intravenous injection of 2 U of insulin, decreased only slightly in the beginning, but remained low for a long time (Fig. 5).
While we may conclude from the first part of the curve that the resistance to insulin is slightly increased in comparison with that of a normal subject (which is possibly an effect of ACTH treatment) we may conclude, from the fact that the blood sugar values remain at a low level for a much longer time than usual, that there is also a decrease of the glycotrophic factor of the anterior lobe of the hypophysis. The blood pressure is only slightly changed. After 0.5 ml. of a 0.1 per cent solution of adrenaline had been administered, an increase in the blood sugar occurred, as is usual, but at the same time we observed a decrease in the blood pressure which is not usual.

7. Changes in the excretion of uric acid and creatinine.

In a normal subject the ratio uric acid-creatinine excretion after one injection of 25 mg. of ACTH should increase by about 90 per cent while it is only only 20 per cent on an average in patients from Addison's disease (Thorn). The increase of this uric acid-creatinine ratio is due to the increased excretion of
uric acid occurring after the administration of ACTH while the creatinine excretion is not affected.

The significance of the values of the uric acid-creatinine ratio in urine is much more difficult to determine than that of the decrease of the eosinophils in the blood as the values found in cases of a slight adrenal cortex insufficiency and in normal subjects overlap to some extent.

Moreover: a sufficient increase in the uric acid-creatinine ratio may be absent, while adrenal cortex insufficiency is out of the question viz. when the excretion of uric acid is already maximal before the corticotrophic hormone is administered. This may be due to a hyperactive adrenal cortex or to influences outside the adrenal glands, particularly in the case of a decreased excretion or of an increased production of uric acid.

The uric acid content of our patient's urine on July 23rd was 22 mg. per cent, while the creatinine content was 75 mg. per cent. On August 4th these figures were 22 mg. per cent and 45 mg. per cent respectively.

The uric acid-creatinine ratio increased from 0.29 to 0.49 which is an increase of 69 per cent. This is perhaps not due to an increased excretion of uric acid, however, but to a decreased excretion of creatinine, which may also be seen after the administration of corticotrophic hormone (Thorn).

This test does not allow us to draw safe conclusions on the stimulation of the 11-oxysteroid production in our patient.

8. The fasting blood sugar values.

Conn et al. (1949) and Sayers et al. (1949) have shown that ACTH may cause a temporary diabetes mellitus in normal subjects (glycosuria, decreased carbohydrate tolerance, increased fasting blood sugar values). This type of diabetes only slightly responds to protamine zinc insulin.

Mason et al. (1948) could not find any glycosuria in his normal subject receiving 100 mg. daily, but did find an increased resistance to insulin.

Forsham et al. (1948) too did not find any glycosuria with
daily doses of 40 mg., but they did find a slight increase in fasting blood sugar values.

These blood sugar values in our patient did not change under the influence of ACTH and there was no increase in the blood sugar values but rather a slight decrease (cf. Fig. 6).

![Fig. 6. Fasting bloodsugar values during treatment with ACTH.](image)

We want to draw attention, however, to a rather remarkable fact. The blood sugar tolerance curve, made 2½ month after corticotrophic hormone administration, was: 84, 104, 128, 136, 128 in the fasting patient and after ½, 1, 1½ and 2 hrs. respectively. Sheehan states that the blood sugar as a rule does not decrease below this value in the fasting subject, within 2 hrs. and quite often not within 3 hrs. In our opinion this phenomenon is difficult to explain at present, in account of the decreased glycotrophic factor of the anterior lobe of the hypophysis and the decreased gluconeogenesis.

9. The blood pressure.

The blood pressure is normal or below normal in most patients suffering from Sheehan's syndrome. Post-mortem findings agree with this finding. While the adrenal cortex is often described as being as thin as paper, the medulla is almost unchanged.

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As to the blood pressure of our patient we may say that this was hardly affected by the injections. Neither the systolic nor the diastolic pressure changed very much (cf. fig. 7).

![Blood Pressure Graph]

Fig. 7.
Influence of ACTH treatment on blood pressure.

10. Changes in the diuresis.

The diuresis was to some extent influenced by the treatment with corticotrophic hormone. In spite of the fact that the preparation used contained 0.5 U oxytocin per 25 mg., which may lead us to expect no effect or at most an anti-
diuretic effect, the opposite was observed viz. an increase in the diuresis. How this can be explained is not at present clear. Perhaps the increased diuresis is due to an enhanced desoxycorticosterone function following ACTH administration. It is well known that the administration of desoxycorticosterone acetate to dogs causes a slight diabetes insipidus (Winter & Ingram, 1949). Fig. 8 shows the course of the diuresis.

CONCLUSIONS AND SUMMARY

Summarising the results of this experiment, we can draw various conclusions. First of all we may say that we found no reason for supporting the tentative view that a primary cessation of the gonadotrophic function of the anterior lobe of the hypophysis does not primarily occur in our case of Sheehan's syndrome.

It has been shown that F. S. H. content of the urine does not increase under the influence of corticotrophic hormone.

With regard to the adrenal glands we have to consider the various functions separately. We can hardly draw any conclusions from the changes in the desoxycorticosterone function: the change in the electocytes may suggest an increased desoxycorticosterone function. We may also say the excretion of 17-ketosteroids is hardly affected. As to 11-oxysteroids, the quantity found in the urine increased slightly; the circulating eosinophils show a slight but definite decrease; no conclusions can be drawn from the uric acid-creatinine ratio; the fasting blood sugar values suggest a decreased instead of an increased production of 11-oxysteroids. The insulin tolerance test suggests a slight resistance to insulin due to the corticotrophic hormone. As to the possible production of oestrogenic substances by the adrenal glands, we may say that this was not increased by corticotrophic hormone. Before and after the treatment, the quantities of oestrogenic substances excreted were less than 40 U per 24 hrs., probably 0. Hence we have good reason for assuming that the functions of the adrenal cortex responded insufficiently in our patient, proba-
bly because these organs were atrophic. The function of the medulla of the adrenal gland was not affected, i.e. no effect was seen on the blood pressure.

The increased diuresis remains unexplained. As to the general condition of our patient we may say that there was a slight improvement during the treatment; at any rate she felt much better. After the treatment she was undoubtedly worse. The danger of this — short — treatment is that the atrophic adrenal glands become exhausted as they are accustomed to function at a low level.

Even if the function of the adrenal glands improves under the influence of corticotrophic stimulation we still have to face the difficulty of maintaining this stimulus.

ACKNOWLEDGEMENT

We wish to thank Miss J. Bakker for technical assistance and Miss J. de Vries for determination of the 11-oxysteroids.

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