A.C.T.H. IN HYPOPIUITARISM

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Hypopituitarism is a condition which presents a therapeutic challenge. In theory successful treatment demands the replacement of all the hormones of the anterior pituitary. At present there is no method of meeting this demand. In the past the most satisfactory treatment has been an attempt to compensate for the secondary atrophy of the gonads, the suprarenal cortex, and the thyroid by the use of testosterone, deoxycortone acetate, and thyroid extract. With the introduction of A.C.T.H. into clinical medicine there arose an opportunity of replacing at least one of the missing hormones of the anterior pituitary. So far there have been few reports on the use of A.C.T.H. in hypopituitarism. In recent papers Robertson and Kirkpatrick (1951) and Summers and Sheehan (1951) have reviewed the position and reported their own experiences. In most cases there was subjective improvement, but in the two cases described by Summers and Sheehan the picture was complicated by the occurrence of migraine and hemiparesis. The biochemical effects of treatment have been less constant. This paper reports the use of A.C.T.H. for short periods in three cases of hypopituitarism.

Case Notes

Case 1.—A man aged 62 had suffered from typical hypopituitarism for five years. The illness began with a period of severe headache, pyrexia, and stiffness of the neck. These symptoms lasted for three weeks and were succeeded by the signs of hypopituitarism. Presumably his pituitary was damaged by an infective lesion. His speech and movements were slow and his limbs stiff, he was perpetually sleepy, he had been impotent for five years, he had a very poor appetite, and was intensely sensitive to cold. He had mild angina of effort and may have had a small myocardial infarct one year previously. The skin was dry and the muscles were flabby. There was no hair on the chest or in the axillae; the pubic hair was scanty and the external genitalia had atrophied. The scalp hair was very fine and silky. The basal metabolic rate was -35% . An intravenous injection of 1.5 units of soluble insulin produced severe hypoglycaemic symptoms. The 17-ketosteroid excretion was 1.5 mg./24 hours.

Case 2.—A man aged 59 had a large sella turcica with erosion of the clinoid processes. For one year he had been very sensitive to cold, had had stiff legs, a hoarse voice, and a very poor appetite. He was apathetic, slow, and unco-operative. There was no hair in the axillae or on the chest, the testes had atrophied, and the pubic hair was scanty. His face was pale and the scalp hair very fine. The visual fields were unimpaired. The basal metabolic rate was -27% and the 17-ketosteroid excretion 1.9 mg./24 hours. Presumably he was suffering from a chromophobe adenoma of the pituitary.

Case 3.—A woman aged 48 suffered from a severe post-partum haemorrhage after the birth of her third child 16 years previously. Since then she had been tired and had slept a great deal. Lactation did not begin after delivery, and there had been only two brief episodes of vaginal bleeding in 16 years. She had been unconscious for 10 days after a minor operation 10 years ago. She spoke very slowly,

had a poor appetite, was very sensitive to cold, and was apathetic but co-operative. The axillae were hairless, her face was pale, and the haemoglobin was 68% (Sahli). The 17-ketosteroid excretion was 3.3 mg./24 hours and the basal metabolic rate -35% . She was suffering from hypopituitarism due to a post-partum necrosis of the pituitary.

Treatment

In each case A.C.T.H. was administered for a period of 10 days after a control period of similar duration. Case 1 received a second course, for seven days, after a further control period. None of the patients had had previous hormonal therapy, and none received any other treatment during the time when A.C.T.H. was given. Case 1 received 25 mg. of A.C.T.H. by intramuscular injection twice daily, Case 2 had 25 mg. thrice daily, and Case 3 had 12.5 mg. four times daily. The A.C.T.H. was that marketed by Messrs. Armour under the name of "acthar."

Results

Subjective Changes.—In each case the most striking clinical result was a great subjective improvement. This took the form of a decreased tendency to fall asleep, the disappearance of much of the stiffness of the limbs, a more rapid speech, and a decrease in the sensitivity to cold. Case 1 felt hungry for the first time in five years. He was able to cut a caper on the floor of the ward, whereas he had only walked slowly and stiffly before having A.C.T.H. Case 2 changed from an unco-operative, apathetic, and rather surly fellow, who did not want to remain in hospital, into a grateful, helpful, and appreciative patient. Case 3 became loquacious and even a little argumentative instead of the dull silent woman she had been. She volunteered that she would like to go for a long walk, an idea that had not occurred to her for many years. These changes were much appreciated by the patients, who all said that they felt better than they had done for a long time. The improvement was not apparent for the first two days of treatment, but began on the third day and was maintained until about three days after the treatment ceased, when it began to decline. Testosterone and thyroid treatment was started before the relapse was complete.

Weight.—Both Cases 1 and 2 showed an increase in weight of 2 kg. during the second half of the period of treatment. In Case 3 the weight fluctuated considerably while treatment continued, but did not show an overall increase.

Clinical Signs.—No patient showed any considerable change in the pulse rate or blood pressure, though there was a small increase in the pulse pressure in Case 1. This patient developed slight ankle and sacral oedema on the last day of his treatment. At the same time his angina of effort was more easily produced. The electrocardiograph did not record any change in Cases 1 and 2. It was not used in Case 3. There was no significant alteration in the haemoglobin level of any patient.

Eosinophil Counts.—Fig. 1 shows the eosinophil counts in the three patients. The counts were done by the method of Roche, Thorn, and Hills (1950). They were made four hours after the first injection of A.C.T.H. each day during treatment and at the same time of day during the control period. In two patients there was a fall in the eosinophil counts. In Case 1 the fall began on the third day of treatment. In Case 3 it began on the seventh day. In Case 2 it is difficult to say whether or not a significant effect was produced, as unfortunately the number of counts performed before treatment was inadequate.

Capillary Resistance.—In Case 1 the capillary resistance was measured before, during, and after the second course of treatment by the method of Robson and Duthie (1950). The readings are shown in Fig. 2. There was a significant increase in the capillary resistance, beginning on the fourth day of treatment. These measurements were not made in the other two patients.

FIG. 1.—Eosinophil counts in three patients.

FIG. 2.—Capillary resistance readings in Case 1.

Carbohydrate Metabolism.—Insulin-sensitivity tests were done in Case 1. Capillary blood was used and the sugar was estimated by the method of Hagedorn and Jensen. In a test done before A.C.T.H. was given, an intravenous injection of 1.5 units of soluble insulin caused the blood sugar to fall from 105 to 44 mg. per 100 ml. in 30 minutes and produced severe hypoglycaemic symptoms, showing that the patient was very sensitive to insulin. On the tenth day of treatment with A.C.T.H. a larger dose of 2.5 units of insulin caused the blood sugar to fall from 114 to 74 mg. per 100 ml. in 45 minutes and produced no symptoms. This indicated a decrease in the sensitivity to insulin.

Glucose-tolerance tests were done before and during treatment in the three patients. The tests were performed in the

early morning: 50 g. of glucose was administered by mouth, venous blood was used, and the estimations of sugar were made by the method of Hagedorn and Jensen. There was no constant change in the glucose-tolerance tests during treatment with A.C.T.H.

Hormone Excretions.—Urinary 17-ketosteroid levels were estimated in the three patients before and during treatment with A.C.T.H. by the method of Callow, Callow, Emmens, and Stroud (1939). In Cases 1 and 3 there was no significant change in the levels during treatment. Case 2 showed an increase from a daily average of 1.5 mg. before treatment to a daily average of 3.4 mg. during the latter half of treatment.

Chloroform-extractable formaldehydogenic corticoids were estimated in the urine of Cases 1 and 3 before and during treatment by a modification of the method of Daughady, Jaffe, and Williams (1948). Because of the known deficiencies of such methods (Marrian, 1951) it is thought to be inadvisable to publish any figures for the corticoid excretion. However, the estimations indicated that in Case 1 the urinary excretion of these corticoids was approximately doubled during treatment, while in Case 3 it was increased by about 50%. In Case 1 the increase began on the second day of treatment, and in Case 3 on the third day.

Conclusions

The subjective improvement in each patient was very striking. As A.C.T.H. is not known to have any action other than that of stimulating the adrenal cortex it is probable that these subjective changes were due to the action of adrenocortical hormones produced in response to the stimulus of A.C.T.H. Objective evidence of an increase in the production of adrenocortical hormones was obtained by some of the tests described. There was an increase in weight in two patients and a fall in the eosinophil count in two. The capillary resistance increased and the insulin sensitivity decreased in the one patient in whom these were measured. There was an increase in the urinary 17-ketosteroid excretion in only one of the three patients. The urinary corticoid excretion increased in the two patients in whom this was estimated. It is thus fair to conclude that the adrenal cortices of these three patients responded to the stimulus of a few injections of A.C.T.H. by increasing their output of steroid hormone.

The only undesirable effects produced were the development of slight oedema and the mild aggravation of the angina in Case 1. This might well have become more serious if the treatment had been continued. It is impossible to judge the value of a long period of A.C.T.H. treatment in hypopituitarism from the results in these patients, and further work will have to be undertaken for this purpose.

Summary

Three patients suffering from hypopituitarism were treated for periods of ten days with A.C.T.H.

In each patient there was a dramatic subjective improvement during treatment. Various objective signs of an increase in secretion of adrenocortical hormones were obtained, such as an increase in weight, a fall in eosinophil counts, a decrease in insulin sensitivity, an increase in capillary resistance, and an increase in urinary corticoid and 17-ketosteroid excretions.

In one patient oedema developed and a pre-existing angina was aggravated.

It is concluded that the adrenal cortices of these patients responded to the stimulus of A.C.T.H.

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ADDENDUM.—Since this paper was written three further cases of hypopituitarism have been given A.C.T.H. Two had post-partum Simmonds's disease, and the other had had a chromophobe adenoma which had been treated surgically and with pituitary irradiation. A.C.T.H. was given in doses of 12.5 mg. every six hours by intramuscular injection. All the patients showed both subjective and objective improvement, and the only undesirable effect was slight oedema in one case.

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TUBO-UTERINE IMPLANTATION*

BY

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Practitioners and consultants alike are often confronted by a patient who gives a history of miscarriage, one pregnancy, one curettage, or one caesarean section, and yet of never again being able to conceive. Close investigation will almost invariably elicit the fact that the abortion was induced or that the pregnancy was followed by a few days of fever which quickly yielded to antibiotics or chemotherapy. When seen months or maybe years later rarely is it possible to palpate anything abnormal in the pelvis, though further study with Rubin's kymograph will show that no gas passes even at high pressures, and that the area of distension pain is low and entirely central, indicating that the blockage is at the internal ostia (Fig. 1), a conclusion even more definitely confirmed by lipiodologram.

FIG. 1

* Address delivered at the All-India Surgeons' Conference in Calcutta, December, 1951.

In some parts of France and the United States of America further proof, as well as valuable information regarding the morbid anatomy of the tubes and ovaries, is thought to be obtained by culdoscopy or coelioscopy (Decker and Cherry, 1944). In this country, however, when the history is that of an induced abortion or infected pregnancy, and gas and oil investigations have been systematically carried out, it is almost invariably the rule to find at laparotomy in 82% that the isthmial and interstitial portions of the tube are alone impermeably sclerosed, whereas the distal parts of the ampullae and fimbriae are perfectly healthy (Fig. 1)—a condition almost pathognomonic of infected secundines. Very occasionally the same morbid anatomy may be present with a history of gonorrhoea, but in these cases there will always be found peritubal as well as periovarian adhesions, conditions often stultifying a good prognosis.

Implantation in the Past

Hitherto, salpingostomy or tubo-uterine implantation has raised scant enthusiasm among gynaecologists. Indeed, as Te Linde (1946) remarks, such operations are practised sometimes by some, rarely by others, and never by many. In the past, the reasons for such an attitude of mind have been (1) that the necessary apparatus for investigation of the patient before and after operation was wanting; (2) the previous history was thought too unreliable for an exploratory laparotomy; (3) the time and labour consumed were not justified by results; (4) the technical skill for a finicky plastic operation was lacking; and (5) the essential instruments were not forthcoming.

But perhaps the real death warrant lies at the door of Greenhill (1937), who, despite Solomons's (1936) questionnaire, sent a similar document to 107 leading American gynaecologists. Of these, 56% utterly condemned all plastic operations on the tube. The remaining 44% had, however, among them performed 818 operations, which altogether had resulted in only 54 pregnancies (6.6%), and from these only 36 live babies were born (4.4% success), for 18.5% aborted and 14.8% were ectopic pregnancies.

Such dismal results, recorded of course long before the era of antibiotics and chemotherapy, should neither depress us nor nowadays be accepted, for, as a result of much trial and careful attention to detail, the pathway is now floodlit for all to follow. Indeed, Raoul Palmer (1951), in a recent follow-up of 26 personal cases in which he had done a tubal implantation alone for the reasons specified, records eight full-term pregnancies and one ectopic, a 37.5% birth success; whereas in 18 other cases in which salpingolysis or salpingostomy was done the pregnancy success rate was only 11%. This figure corresponds with our own experience; for a fimbrial or ampullary block, with or without a hydrosalpinx, implies a pathological endosalpinx unfavourable to the passage of an ovum, whereas a clear-cut tubal implantation denotes, as a rule, a healthy mucous membrane beyond the block at the isthmus. In the 10 full-term pregnancies which Palmer records following 44 operations, caesarean section was necessary in only three. Moreover, in his latest 20 cases he has had six full-term pregnancies (30%) and no ectopics.

Such small numbers and short-term statistics are rightly looked at askance, but when they are backed by personal experience and that of many others in this country they surely challenge emulation.

Method of Tubal Implantation

Many techniques have been tried, with varying success. I advocated (Green-Armytage, 1937) the coronal uterine incision which had been advised by Bonney (see Bonney, 1947): in this the implanted tube is threaded with silk-worm gut, which is brought down into the vagina. Later, ureteric catheters and stainless silver wire were employed