EFFECT OF INTRAMUSCULAR INJECTION OF PITUITARY TISSUE IN RHEUMATOID ARTHRITIS

BY

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Pituitary gland implants from other than an identical twin cannot be expected to function in man, whether the source be man or animal, but may act as a temporary source of hormone because of their ACTH content. The gland also contains other hormones and may be better than ACTH because of the slow absorption of hormone. Favourable results have been reported by Edström (1950) and Edström and Thune (1951). We therefore decided to test the efficacy of pituitary implantation in patients suffering from rheumatoid arthritis, determining the ACTH content of the implant, the clinical changes, and the adrenal response compared with that of ACTH.

Materials and Methods

(1) Technique.—The calf hypophysis was removed under sterile conditions and cleaned 30 to 60 minutes after death. One part of the pituitary was homogenized with physiologic saline and another was cut up into five to six pieces of similar size. The homogenate and the minced tissue were injected intraglutely with 200,000 units penicillin. Ejection of the implant occurred in one case and allergic reaction in none.

(2) ACTH Activity of the Implant.—The ACTH activity of the pituitary homogenate in 0.9 per cent. NaCl solution pH 1.0 was determined in various dilutions by the ascorbic acid depletion test of Sayers, Sayers, and Woodbury (1948) using corresponding dilutions of Cortrophin Z (Organon-OSS) as standard, without the addition of a precipitating agent, as described elsewhere (Forgács and Hajdu, 1956). The calf pituitary homogenate was found to be as active as about one twenty-fifth of its weight of the standard ACTH employed.

(3) Classification of Patients.—This was based on the grades described by Steinbrocker, Traeger, and Batterman (1949), except that Stages I and II were taken together as Group A (capable of full normal joint function or with a slight restriction of motion in one or more joints due to articular pain; osteoporosis; limited subchondral bone destruction; slight joint swelling; moderate muscle atrophy; extra-articular changes such as tendovaginitis, peri-arthritis, etc.).

Group B patients were those in whom impaired function interfered with normal activity so that they were only partially capable of caring for themselves, and showed subchondral rarefaction or destruction of bone, marked muscle wasting, and extra- and intra-articular changes.

Group C comprised completely helpless patients, confined to bed or chair, with severe x-ray destruction, muscle wasting, joint deformity, contractures, subluxations, or ankylosis.

(4) Plan of Study.—Patients were treated as hospital in-patients over a period of about 4 weeks and received the following injections at weekly intervals:

(i) 20 I.U. long-acting depot ACTH;
(ii) Homogenate and minced pituitary (as described);
(iii) Placebo (saline);
(iv) Brain tissue homogenate.

The order of the injections was varied.

(5) Evaluation of Clinical Response.—Marked improvement, designated "++" in the Table, signifies decrease of pain and restoration of mobility, slight improvement is designated "+", and no improvement or deterioration is designated "0".

(6) Evaluation of Adrenocorticoid Response.—A marked adrenal response (designated "+++")
was defined as a mean urinary 24-hr output of 17-ketosteroids (by Callow’s method—see Hajdu and Forgács, 1954) on the 3 days after the start of treatment more than twice that of the preceding resting output. A slight adrenal response was defined as a mean increased output of at least 50 per cent. of the control level, and no response was defined as less than this.

Results
The results are shown in the Table, which shows that pituitary implant failed to produce any more improvement than that produced by control injection, which in turn was itself inferior to that produced by ACTH. There was little or no adrenal response with any of the three treatments. Clinical response was more marked with each treatment in patients in Group A than in those with further advanced disease (Groups B and C).

Discussion
Hypophysitis implants introduced in 1937 (Kylin, 1937) have been claimed to benefit not only various endocrine conditions (Westman, 1941; Westman and Jacobsohn, 1942; Edström and Westman, 1942), but also skin diseases (Kühnau, 1952; Vámos, Szendei, and Márton, 1952), trigeminal neuralgia (Bues, 1952), peptic ulcer (Schubert, 1955), and cancer (Gumrich, 1951; Martyn, Simon, and Vizián, 1957), as well as rheumatoid arthritis (Edström, 1950), mainly after the introduction of ACTH by Hench in the U.S.A. Most of these studies came from Europe at a time when ACTH was not generally available, and although they report favourable results they lack critical value (compare Fellinger and Schmid, 1952, who give an account of 6,000 implantations in 1,400 cases). Thus a controlled study like this becomes a necessity and has shown no difference between the cases on treatment and those on placebo.

Summary
The therapeutic and endocrine efficacy of hypophysitis hetero-implantation has been studied in 20 carefully observed patients with rheumatoid arthritis, using as a control saline or brain tissue implantations. The results were compared with the response to 20 I.U. ACTH. ACTH produced clinical improvement, but this was seen in only a few of those treated with pituitary implant and paralleled the number of improvements seen in those treated by placebo or control. Hypophysitis implantation seems to be no better than placebo therapy.

REFERENCES

Table
CLINICAL AND ADRENAL CORTICAL RESPONSES TO DIFFERENT TREATMENTS
IN THE THREE STAGES OF THE DISEASE

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Effet de l'injection intramusculaire de tissu pituitaire sur l'arthrite rhumatismale

Résumé
On étudia l'efficacité thérapeutique et endocrinienne des greffes hétérogènes d'hypophyse sur 20 malades atteints d'arthrite rhumatismale et soigneusement observés, l'eau physiologique et des greffes de tissu cérébral servant de substances-témoins. On compara les résultats à ceux obtenus avec 20 unités internationales d'ACTH. Cette hormone produisit une amélioration clinique qui ne se manifesta que chez quelques malades traités par la greffe pituitaire et chez un nombre correspondant de ceux traités par les substances-témoins. Il apparaît donc qu'une greffe pituitaire n'a aucun avantage sur une substance-témoin.

Effecto de la inyección intramuscular de tejido pituitario sobre la artritis reumatoide

SUMARIO
Se estudió la eficacia terapéutica y endocrina de heteroinjertos de hipófisis sobre 20 enfermos con artritis reumatoide, cuidadosamente observados. El suero fisiológico e injertos de tejido cerebral sirvieron como substancias de control. Se compararon los resultados a los obtenidos con 20 unidades internacionales de ACTH. El tipo de mejoría obtenido con la ACTH se vió tan sólo en pocos casos tratados con el injerto pituitario y otros pocos tratados con las substancias de control. Se concluye que un injerto pituitario no tiene ventaja alguna sobre substancias de control.
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