

Effect of ACTH on Wound Healing in Humans.* (17867)

MORTON C. CREDITOR, MARGARET BEVANS, WILLIAM L. MUNDY, AND CHARLES RAGAN

From the First (Columbia) Research Service, Goldwater Memorial Hospital, and the Department of Medicine, Columbia University College of Physicians and Surgeons, New York City.

In an earlier report(1), the chance observation of delayed healing of wounds in patients on adrenocorticotrophic hormone (ACTH) therapy was noted. These wounds had occurred as a result of complications unrelated to the basic disease being treated with ACTH. In a later report(2), controlled studies in rabbits were recorded and again delay in connective tissue formation in cortisone treated animals was noted. It is the purpose of this report to present the results of controlled studies in human subjects.

In 2 patients treated with ACTH* (one with periarteritis nodosa and one with rheumatoid arthritis) elliptical skin biopsies were made on the first day of therapy. The

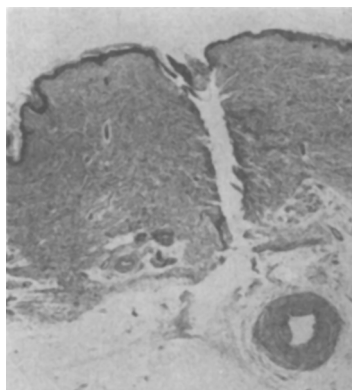


FIG. 1.
One-week-old skin wound from patient on ACTH: Hematoxylin and eosin, $\times 11$.

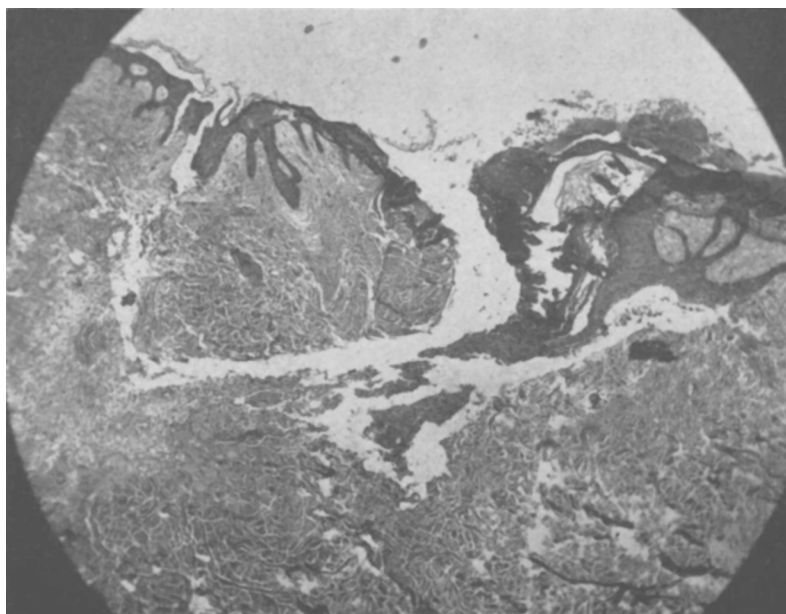


FIG. 2.
One-week-old skin wound from patient on ACTH. Hematoxylin and eosin, $\times 38$.

* Aided in part by a grant from the Masonic Foundation for Medical Research and Human Welfare.

1. Ragan, C., Grokoest, A. W., and Boots, R. H.,

Am. J. Med., 1949, v7, 741.

2. Ragan, C., Howes, E. L., Plotz, C. M., Meyer, K., and Blunt, J. W., *PROC. SOC. EXP. BIOL. AND MED.*, 1949, v72, 718.



Fig. 3.
One-week-old incised wound 1 week after cessation of
ACTH. Hematoxylin and eosin, $\times 38$.

wounds were closed with silk and after one week the whole area was excised. The dose of ACTH during this time was 100 mg per day on the first day and 40 mg per day thereafter. Under normal circumstances such wounds should be either healed or show evidences of advanced granulation tissue formation after one week.

Fig. 1 and 2 are photo-micrographs of the re-biopsied wounds. As can be seen in cross section, there is no evidence of healing of the mesenchymal tissues. A small amount of fibrin is seen between the wound edges. There is proliferation of epithelial structures, but practically no granulation tissue, leucocytes, fibroblasts or proliferating blood vessels are evident. One week later and one week after

cessation of ACTH, the wound sites were re-examined. The first patient's wound was grossly healed and in the second a re-biopsy was performed as a further control. Histologically, the normal healing was evident (Fig. 3).

In an attempt to reverse this action of ACTH an additional experiment was performed. Seifter *et al.*(3,4) have implied, as a result of *in vitro* and *in vivo* studies, that cortisone and certain other steroids cause inhibition of hyaluronidase activity. It was therefore postulated that hyaluronidase activity might be necessary for proper wound healing and that inhibition of such activity might have been responsible for the observed

* The ACTH used in this study was generously supplied by Dr. John R. Mote of the Armour Laboratories.

3. Seifter, J., Baeder, D. H., and Dervines, A., *PROC. SOC. EXP. BIOL. AND MED.*, 1949, v72, 136.

4. Seifter, J., Baeder, D. H., and Begany, J., *PROC. SOC. EXP. BIOL. AND MED.*, 1949, v72, 277.

effects of ACTH. Therefore, in a 45-year-old female patient with rheumatoid arthritis on ACTH, an incised wound 2 cm long and about 1.5 cm deep was made on the lateral aspect of the right thigh. An ethylene plastic catheter corresponding in size to a 20-gauge needle was inserted obliquely into the wound and the wound edges were then closed with silk around the catheter. Using aseptic precautions the wound was irrigated through the catheter 6 times daily with 0.5 cc of a solution containing 90 turbidity reducing units of bull testes hyaluronidase[†] and 50,000 units of penicillin.

In this rather gross manner an attempt was made to supply an excess of exogenous hyaluronidase to the tissue which might be theoretically depleted in endogenous enzyme. On the opposite leg a control incision was made and irrigated with penicillin solution alone. After 4 days both wounds were excised. The control wound appeared much the same as those described above. The

hyaluronidase-treated wound appeared to be healed grossly. After removal of the sutures the wound edges adhered. Fig. 4 is a photomicrograph of a cross section through the wound. The wound edge is bridged by a continuous layer of epithelium. However, the subepithelial layers are filled only with fibrin with no evidence of fibroblastic activity. Incised wounds of rabbits treated with cortisone have also failed to heal when hyaluronidase was injected locally into the wound.

The significance of this "false healing" is unknown and may have been merely fortuitous. However, it does illustrate that, in spite of epithelialization and superficial evidence of gross healing, "true healing" in terms of fibroblastic activity failed to occur.

In all of the patients studied the usual clinical and laboratory evidences of hyperadrenalism occurred. Dramatic improvement in the disease processes took place. The circulating eosinophile counts dropped significantly. The erythrocyte sedimentation rates fell and the characteristic electrolyte and uric acid excretory changes were seen.

Discussion. These observations indicate that wound biopsies provide a readily available means for study of the actions of ACTH upon tissues. Moreover, wound healing may be considered a type of tissue reaction somewhat analogous to that abnormally occurring in the mesenchymal diseases susceptible to therapy with ACTH. As such, it constitutes a tool for further study of the mechanism of the therapeutic effects of ACTH.

Summary. Observations are presented indicating that during hyperadrenalism induced by ACTH there is inhibition of wound healing in humans. The value of these observations as a means of studying the effects of hyperadrenalism at the tissue level is implied.



FIG. 4.
4-day-old wound locally treated
with hyaluronidase (see text).
Trichrome stain, $\times 68$.

[†] Supplied as "Hydase" by Wyeth Co.