Regression of Experimental Skin Tumors in Mice Following Local Injections of 17-Hydroxycorticosterone-21-acetate*

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It was shown in 1953 by Engelbreth-Holm and Asboe-Hansen (4) that cortisone, injected intraperitoneally, caused a definite reduction in the development of tumors and an increased latent period in albino mice of strain ST/Eh painted once with 9,10-dimethyl-1,2-benzanthracene (DMBA). Similar results were obtained by Boutwell and Rusch (8) with carcinomas induced by benzpyrene. Sulzberger, Herrmann, Piccagli, and Frank (8) found that repeated subcutaneous injections of cortisone increased the incidence of skin tumors induced by methylcholanthrene in albino mice of a Swiss strain.

The adrenal cortical steroid cortisone is known to exert an effect on the fibroblasts (6, 7), on the ground substance, and the mast cells (1, 2, 9), and thus on the connective tissue as a whole. Only a few reports have been published on alterations in ectodermal tissues caused by adrenal cortical steroids. Green and Ghadially (5) found that cortisone inhibited the mitotic activity in mouse epidermis. This did not, however, apply to epidermis painted with 9,10-dimethyl-1,2-benzanthracene. In tumors the mitoses were also found to be resistant.

The connective tissue of skin tumors (precancerous papillomas) induced by 9,10-dimethyl-1,2-benzanthracene contains enormous quantities of mast cells (4). Their presence in the connective tissue of tumors is worth noting, as mast cells are presumed to produce a ground-substance component of the hyaluronic acid and heparin type which probably influences the permeability of the connective tissue (1, 2).

The role of connective tissue in skin carcinogenesis still remains to be elucidated. However, since in systemic therapy cortisol has affected skin carcinogenesis and since this hormone exerts its main effect on the connective tissue, we started experiments consisting of the injection of 17-hydroxycorticosterone-21-acetate (hydrocortisone or Kendall's compound F) into fully developed tumors induced by DMBA in mice. The local effect of hydrocortisone on connective tissue is assumed to be similar to that observed following systemic administration of cortisone.

MATERIALS AND METHODS

In a preliminary experiment we used a total of 44 albino ST/Eh female mice1 ranging in age from 3 to 7 months. The mice were painted once on the dorsal skin with 0.05 ml. of a 0.5 per cent solution of 9,10-dimethyl-1,2-benzanthracene. Papillomas developed in 31 mice. In fifteen of these a microcrystalline suspension of 17-hydroxycorticosterone-21-acetate2 (1 mg. in 0.1 ml. of suspending fluid) was injected under slight pressure into the connective tissue beneath the tumors once weekly for 7 weeks. The remaining sixteen, which served as controls, were given similar injections of the same quantity of physiological saline solution, with the following result: The tumors disappeared in ten out of the fifteen mice treated with compound F but in only three of the sixteen control mice.

This difference seemed significant, but the groups were too small and the mice too heterogeneous. The experiment was, therefore, repeated with 200 8-week-old albino mice—60 females and 140 males. These mice were divided into two groups of 100 each (30 females and 70 males) and painted as described above. Twenty-one to 35 days after the painting, papillomas were observed in 123 mice, 58 of one group and 65 of the other. When the tumors were 7–10 days old the experiment proper was started.

1 Mice of strain ST/Eh were kindly supplied by Professor J. Engelbreth-Holm, M.D., of the University Institute of Pathological Anatomy, Copenhagen.

2 Manufactured and kindly supplied by Leo Pharmaceutical Products, Copenhagen. The preparation has a crystalline size of 5 μ and is suspended in physiological saline.
started. The group of 65 mice was treated with hydrocortisone acetate injected into the connective tissue underlying the tumors, whereas the group of 58 was given injections of the suspending fluid (physiological saline solution).

**RESULTS AND CONCLUSION**

After 7 weeks' treatment 83 per cent of the tumors of the mice treated with hydrocortisone and 36 per cent of the tumors of the control mice had disappeared (Table 1). In the control group the number of tumors subsided evenly until the 6th week, while in the treated group the most marked change took place after the third injection. The treatment was stopped after 7 weeks. After 14 weeks the number of tumors present was the same as after 7 weeks.

Hydrocortisone acetate, administered as local injections, makes experimental skin tumors—precancerous papillomas—subside. It is evident that the percentage of regression was far higher in the male than in the female group, but the spontaneous regression rate was also higher in the males. The strongest response to hydrocortisone was given by the female mice. The percentage of takes was 73 in females and 56 in males. After the tumors had disappeared, the skin was apparently normal, but rather thin.

Further studies on the point of attack of the steroid in causing regressions and the probable mechanism of the effect are in progress.

We realize that injections of physiological saline solution into the controls did not afford a physical effect on the tissue similar to that of the relatively coarse steroid particles. Nevertheless, we chose this procedure as a control of the injections themselves and deliberately did not use substances that might be presumed to approach the physical effect of hydrocortisone acetate without possessing its chemical properties. In that case, we would have been dealing with foreign-body reactions, and such reactions are not induced by hydrocortisone.

**SUMMARY**

Of 123 albino mice of strain ST/Eh with skin papillomas induced by one painting with 9,10-dimethyl-1,2-benzanthracene, 65 were injected topically with 17-hydroxy cortisol-21-acetate (hydrocortisone, compound F) once weekly for 7 weeks. Fifty-eight controls received injections of physiological saline solution. Eight weeks after the first injection 83 per cent of the tumors of the treated mice and 36 per cent of the tumors of the control mice had disappeared. Topical treatment of the experimental tumors caused unmistakable regression. The strongest response to hydrocortisone was noted in the female mice.

**REFERENCES**

Regression of Experimental Skin Tumors in Mice Following Local Injections of 17-Hydroxycorticosterone-21-acetate

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