canine Heidenhain pouches. Although their chemical composition has not been established, there is reason to believe that they are neither pepsinogen, pepsin, nor one of the mucins.

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Effects of Cortisone and 11-Desoxycortisone on Pain Thresholds in Man.* (18916)

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While testing 11-desoxycortisone† in allergic disorders, it was noted that the tooth pain thresholds of 5 patients decreased with this steroid medication. Thus the patients, over a period of hours, were able to recognize a smaller stimulus. Since these patients were not trained, the decreases in pain thresholds could be, and tentatively were, interpreted as a normal learning curve. Because cortisone and also ACTH therapy occasionally produce euphoria and other psychic changes(1,2), it is remotely possible that the mechanism of the analgesic effect of cortisone is similar to that of the opiates.

Method. To test these hypotheses, trained subjects were used to assay the effects on pain thresholds of 11-desoxycortisone and cortisone. As a control for this study a placebo (cholesterol) was administered. Absolute blind test conditions were used in that the vials of suspended steroid were labeled A, B, and C and the identity of the injected suspension was unknown both to the experimenter and the subjects.

Four trained male subjects were used for these tests. At the beginning of each experiment 2 or more control pain thresholds were determined with both the tooth and warm wire algesimeters. The saline suspension of steroid (25 mg) was administered by intramuscular injection and the pain thresholds were then measured at hourly intervals for 6 hours. The experimental period extended over 7 hours and the subjects were permitted to resume their usual activities between pain threshold determinations. Each of the 4 subjects received 11-desoxycortisone, cortisone, and the placebo (cholesterol) at weekly intervals in an arbitrary but varied sequence. Two types of algesimeters were used: the warm wire algesimeter of Lee, Williams, and Pfeiffer(3), and the tooth algesimeter of Goetzl, Burrill, and Ivy(4). The warm wire algesimeter consists of a nichrome resistance wire (crimped to provide a tip for application of the stimulus) in series with a milliammeter, a rheostat, and a source of electrical current. The current was varied by means of the rheostat. The instrument was calibrated in increments of 10 milliamperes with a range of 400-1000 milliamperes. The conduction heat stimulus was applied to the skin of the volar surface of the wrist. The tooth algesimeter provided induced alternating current as a secondary coil was moved toward a rotating primary coil. The calibration was in increments of 0.2 volt with a range of 0 to 4.2 volts The induced electrical stimulus was applied to the filling of a tooth. Two pain thresholds were determined with the algesimeters. Using the warm wire algesimeter on the skin of the volar surface of the wrist, the wrist pain threshold was

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† Compound S of Reichstein.

1. Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F., *Arch. Int. Med.*, 1950, v85, 545.

2. Boland, E. W. and Headley, N. E., *J. A. M. A.*, 1949, v141, 301.

3. Lee, R. E., Williams, H. L., and Pfeiffer, C. C, *Fed. Proc.*, 1949, v8, 314.

4. Goetzl, F. R., Burrill, D. Y., and Ivy, A. C., *Quart. Bull. Northwestern Univ. Med. School*, 1943, v17, 280.

determined. The wrist was immersed in a 40°C water bath for one minute just prior to testing. The wrist threshold was taken as the milliamperage which consistently produced 3 painful stimuli with 3 applications of the wire. The stimulus was applied to the same spots unless they became erythematous or altered in sensitivity as compared with adjacent areas. The subject was made aware of the sensation of touch with a cool wire stimulator to prevent confusion of touch with slight pain. With the tooth algesimeter 2 endpoints are frequently used. The first is the perception of a non-painful sensation and the second is the perception of true pain. In these experiments the endpoint was the perception of true pain. For a description of the method of determining the tooth pain threshold see the report of Sonnenschein, Jenney, and Pfeiffer(5).

The data were subjected to statistical analysis applying Student's "t" as described by Snedecor(6). The pain threshold alteration produced by 11-desoxycortisone or cortisone was compared in each individual with the alteration produced by the placebo (cholesterol) in the same individual. A test of significance was made of the mean of these differences. The usual confidence level of 5% was employed.

Results. 11-desoxycortisone did not significantly alter the wrist pain threshold, but it did lower the tooth pain threshold significantly. The tooth threshold decreased gradually to the lowest reading 5 hours after the injection. These results are summarized in Table I. Cortisone did not significantly alter the wrist or tooth pain thresholds (Table I). The threshold alteration produced by 11-desoxycortisone was compared in each individual with the alteration produced by cortisone in the same individual. The significance of the mean of these differences was determined. The differences between the alterations of the wrist and tooth pain thresholds produced by 11-desoxycortisone and cortisone were not significant (Table I).

TABLE I.

	Hr after inj					
	1	2	3	4	5	6
Effects of 11-desoxycortisone on pain thresholds (25 mg in 4 subjects)						
Pain threshold	*	*	*	*	*	*
Tooth (volts)	−.25	−.28	−.33	−.35	−.38†	−.13
Wrist (m.a.)	5	−12.5	−2.5	2.5	17.5	5
Effects of cortisone on pain thresholds (25 mg in 4 subjects)						
Pain threshold	*	*	*	*	*	*
Tooth (volts)	−.18	−.15	−.10	−.05	.08	−.05
Wrist (m.a.)	0	−17.5	5	0	22.5	35
Comparison of effects of 11-desoxycortisone (25 mg) and cortisone (25 mg) on pain thresholds (4 subjects)						
Pain threshold	†	†	†	†	†	†
Tooth (volts)	.08	.13	.23	.15	.45	.08
Wrist (m.a.)	−5	−5	7.5	−2.5	5	30

* Mean of individual differences between threshold alterations produced by the drug and the placebo in the same individuals.

† Mean of individual differences between threshold alterations produced by 11-desoxycortisone and cortisone in the same individuals.

‡ Statistically significant, *i.e.*, probability for random selection calculated from "t" values for the mean differences is less than 5%. (P = <.05).

(m.a.) = milliamperes.

The side effects reported to the operator after the injection of these agents were as follows: After cortisone, Subjects 1 and 2 experienced headache, and Subjects 2 and 3 experienced euphoria; after 11-desoxycortisone, Subject 2 experienced marked sleepiness and xerostomia; and after cholesterol, no symptoms were reported.

Discussion. The lowering of the tooth pain threshold produced by 11-desoxycortisone confirms the previous findings in allergic patients. In the present study, trained subjects were used and a placebo injection was employed as a control under blind-test conditions. This lowering of the tooth threshold can now be interpreted as the effect of the drug rather than the effect of a normal learning curve. However, the wrist pain threshold was not lowered by 11-desoxycortisone. The

5. Sonnenschein, R. R., Jenney, E. H., and Pfeiffer, C. C., *J. Appl. Physiol.*, 1949, v2, 141.

6. Snedecor, G. W., *Statistical Methods*, Iowa State College Press, Ames, 1946, p. 43.

only other compound which is known to lower the pain threshold is ergotamine tartrate. This agent lowers the tooth pain threshold and also the warm wire pain threshold.

Cortisone failed to raise the pain thresholds although euphoria was experienced by 2 of the 4 subjects. These results do not support the hypothesis that cortisone produces analgesia by the same mechanism as the opiates. Cortisone and the antipyretic analgesics have many similar actions. Similar metabolic and biochemical effects of cortisone and antipyretic analgesics are(7): 1. antipyretic effect, 2. glycosuria, 3 uricosuric effect, and 4. dilution of blood. On the glycosuria of the depancreatized rat, salicylates have an effect opposite to that of cortisone(8). Both cortisone and the antipyretic analgesics produce pain-relief only in certain selected clinical disorders. Sonnenschein and Ivy(9) found that the elevations of the tooth pain threshold after aspirin were not significant when compared with a lactose placebo. Studies in our laboratory confirmed this failure of aspirin to elevate the tooth threshold and further demonstrated the failure of aspirin to elevate the warm wire pain threshold. However, both the tooth and warm wire methods of algesimetry have demonstrated statistically significant pain threshold elevations in trained subjects with morphine and other analgesics. As cited above, cortisone and the salicylates are similar in many respects and this study indicates one further similarity in that neither produces an increase in pain thresholds.

The potent analgesics act on the physiologic system concerned with pain (the receptors, nerve fibers, synapses, or higher mental centers). However, pain-relief can be effected by agents that remove the pathophysiologic state causing the stimulation of pain receptors. These findings suggest that cortisone, like the salicylates, may produce pain relief by altering pathophysiologic states. That cortisone may alter pathophysiologic states is supported by numerous observations. With cortisone therapy there has been reported: a decrease in the joint swelling of rheumatoid arthritis and acute rheumatic fever; suppression of fever, skin eruption, and serositis in acute disseminated lupus erythematosus; subsidence of ocular inflammation; and a decreased edema in nephritis(10). Further speculation as to the mechanism of clinical pain relief by cortisone must await additional experimental investigation.

Summary. Under the conditions of these experiments, 11-desoxycortisone (25 mg) lowered the tooth pain threshold, but did not alter the wrist pain threshold, and cortisone (25 mg) did not alter the tooth or wrist pain thresholds. An alteration of the pathophysiologic state initiating pain is suggested as an explanation for the pain relief afforded by cortisone.

7. Pfeiffer, C. C., Lee, R. E., Hemmens, E. S., and Hasegawa, A., *Proc. Inst. of Med. of Chicago,* 1950, v18, 96.

8. Ingle, D. J., PROC. SOC. EXP. BIOL. AND MED., 1950, v75, 673.

9. Sonnenschein, R. R., and Ivy, A. C., *J. Pharm. and Exp. Therap.,* 1949, v93, 308.

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Aqueous Humor as a Tissue Culture Nutrient.* (18917)

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Since Harrison(1) first performed experiments on the cultivation of cells *in vitro* using frog lymph, a variety of body fluids has been used in nutrient media. In view of the results of Greene(2) and Browning(3) on the transplantation of tumors and embryonic tissues to