THE EFFECT OF INTRADERMAL INJECTION OF ADRENO-CORTICAL HORMONES*

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How adreno-cortical hormones work is largely unknown, but clinical and experimental evidence seems to show that their action is mainly peripheral. Because it is accessible, we decided to observe the action of these hormones on the human skin.

Our studies include observations on skin flare, pain, sweating, wound healing and spreading of dyes.

FLARE, PAIN, SWEATING

Review of literature: In 1948 Selle (21) working on the rat reported that adrenalectomy increased the histamine content of the tissues and also the sensitivity to histamine. This was confirmed by Dale (7). Carryer (4) used the serum of rabbits previously sensitized to sheep erythrocytes and could not see any effect of cortisone on the release of histamine. Friedlander and Friedlander (10) reported that ACTH does not affect the whealing reaction to histamine or allergens. Recently Michael and Whorton (16) observed that skin flare was inhibited in the croton oil reaction of the rabbit.

Zeller (27) determined the response of allergic patients who were treated with ACTH to various skin tests, and found no change of reactivity even after full clinical relief was obtained. Derbes (8) and others observed that in the positive response to the tuberculin skin test ACTH and cortisone diminish the inflammatory exudate without affecting the qualitative cytologic changes. A number of investigators found that cortisone and ACTH inhibit the inflammatory reaction of the eye to a variety of stimuli. This effect can be obtained by subconjunctival injection of 10 mgm. of cortisone. We have found no reference to direct observation on the effect of these hormones on the flare reaction in human subjects.

Methods: Throughout these experiments intradermal injections of 0.1 cc of a suspension of cortisone acetate (Cortone, Merck & Co.) diluted with saline, so as to contain 5 mg. per cc, and a 5 mg. per cc saline suspension of desoxycorticosterone (DCA), Percorten, Ciba, were used. Intradermal injections of 0.1 cc of saline were used as a control. The subjects were laboratory workers and hospital patients and all tests were made on the back.

In our first experiments we used as a source of heat an electrically heated wire according to Lee, Williams and Pfeiffer (15). This did not allow accurate measurement of the temperature at the point of contact with the skin and the energy necessary to obtain and maintain a given temperature could not be determined. We were fortunate to have made available to us a special instrument designed and built by Dr. Victor Guillemin of the University of Illinois which allows us to measure exactly and control completely temperature and energy input. Technical details will be published in a separate paper.

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At selected sites the hormones were injected intradermally and then stimulated for one minute at 45.6 degrees C with the first apparatus described. The extent of the skin flare surrounding the area of stimulation was noted and the diameter (in mm.) of the different areas compared (table 1). Similarly, we studied the effects of the hormones on the flare produced by histamine 1:600,000 in 9 patients (table 1) and epinephrine 1:100,000 in 5 patients (table 2). The drugs were given as soon as possible after the injection of the hormone. A high dilution was used in order to avoid obliteration of fine differences. The dose was always 0.1 cc and it was injected directly into the wheal of the hormone injection, if possible through the old needle hole.

For the determination of sweating the area was painted with tincture of iodine. 0.1 cc of a 1:100 solution of acetylcholine bromide was injected and starch paper was applied every 20 seconds. The amount of sweating was determined from the degree of coloration of the paper.

TABLE 1

Effect of adreno-cortical hormones on the flare reaction in human skin

NO. OF SUBJECTS	STIMULANT	SALINE AREA	CORTISONE AREA	DCA AREA
5	45.6° C. for 1 minute	24 ± 1.0	19 ± 2.3	28 ± 2.3
9	Histamine 0.1 cc 1:100,000	Wheal 13 Flare 31 ± 2.9	Wheal 13 Flare 22 ± 1.2	Wheal 13 Flare 25 ± 0.9

The numbers in the table give the mean diameter in mm. and the standard errors of the means.

Results: The results (table 1) show that regardless of the nature of the stimulus there was a tendency for inhibition of flare in the cortisone area. Table 2 shows that the vasoconstrictor effect of epinephrine is not affected by the hormones, while the pattern of skin flare is the same as that obtained with other stimuli. In 31 subjects out of a total of 54, the pain from heat stimulation in the cortisone area was reported by the subject to be less than in the saline or DCA area.

Hormones injected locally did not influence the sweating induced by acetylcholine injected locally.

In order to determine whether we were dealing with a local effect of the hormone or with a nonspecific chemical effect, we compared the effects of cholesterol, adreno-cortical extract, cortisone, and the supernatant fluid of cortisone on 5 subjects using histamine as the stimulant. The results (table 3) show that both ACE (adreno-cortical extract) and cortisone inhibit skin flare more than does cholesterol, but the supernatant fluid has even a more pronounced effect than the steroids. Merck & Co. kindly supplied us with pure cortisone powder and the suspending medium used in making the commercial suspension. Using locally the pure cortisone in the saline suspension (5 mg. per cc) and at another site the Merck & Co. suspending medium, we determined the reaction to heat stimulation (45.6 degrees C for one minute). Under these conditions neither of these

two preparations showed any significant effect on the flare response as compared with saline (table 4).

Conclusion: The commercial cortisone preparation produced an inhibition of skin flare, but this effect may be a nonspecific chemical one. The wetting agent used in the suspending medium may be as much responsible for this as the hormone itself. In the majority of the cases tested, there was a marked local anes-

TABLE 2

The effect of the hormones on the skin flare and the vasoconstrictor response to epinephrine (1:100,000) in 9 subjects

	SALINE AREA	CORTISONE AREA	DCA AREA
Vasoconstriction	12 ±0.7	12 ±0.7	11 ±0.9
Skin flare	24 ±4.6	16 ±3.7	21 ±1.9

The values are mean diameter in mm. with the standard errors of the means.

TABLE 3

The effect of various substances on the histamine (1:100,000) flare reaction (5 subjects)

CHOLESTEROL	ACE	CORTISONE	SUPERNATANT FLUID OF CORTISONE
40.2 ±6.6	36.0 ±5.8	36.0 ±6.2	28.2 ±4.5

The values are mean diameters in mm. with standard errors of the means.

TABLE 4

The effect of pure cortisone powder suspended in saline and the commercial suspending medium on the skin flare reaction to heat (45.6° C. for 1 minute) (6 subjects)

CORTISONE	SALINE	SUSPENDING MEDIUM
35 ±2.6	32 ±1.7	33 ±3.7

The values are mean diameters in mm. with the standard errors of the means.

thetic effect of cortisone. Local sweating response to acetylcholine was not affected by any of the hormones.

EFFECT ON WOUND HEALING

Review of Literature: It has been pointed out by a number of investigators that cortisone affects wound healing. Plotz and Howes (18) observed that in patients with mesenchymal disease under treatment with ACTH, wounds heal slowly. Baker (2), too, found that alcoholic adreno-cortical extract impaired wound healing in the rat. Spain and coworkers (22) using cortisone in the mouse corroborated these results. Gross (12) states that cortisone inhibits acute and chronic inflammation otherwise induced by formaldehyde, but DCA

does not prevent this from taking place. He did, however, find that DCA combined with vitamin C produced some inhibition, but less than that of cortisone. Gross' results with cortisone were confirmed by Heilmeyer (14). Shapiro, Taylor and Taubenhaus (23) studied the effect of the presence of certain steroids on turpentine abscesses in the rat. They report stimulation of fibroblastic proliferation by DCA and inhibition by cortisone and sex hormones.

Castor (5) treated rats for a prolonged period with cortisone and showed histologically thinning of the epidermis, cessation of hair growth, regression of glands, loss of collagenous substance from the fibers and reduction of fibroblasts. However, Grant, Grossman and Cornbleet (11) in our laboratory were unable to demonstrate such an effect in human subjects. As both these experiments were carefully controlled, this indicates a pronounced species difference. This is an essential point in the evaluation of the work done in animals, and it shows the need of a large and carefully controlled series in human subjects.

TABLE 5

Heat injury (53.4° C. for 1 minute) immediately after intradermal injection of test substances. Area of injury (mm.) after 5 days

SUBJECT NO.	CORTISONE	SALINE	DCA
1	12 papule	4 macule	3 macule
2	4 macule	2 macule	—
3	5 vesicle	4 macule	2 macule
4	3 papule	—	—
5	6 macule	5 macule	6 macule
6	3 papule	—	—
7	7 macule	3 slight macule	6 very light macule
8	7 central vesicle	5 macule	5 dark macule
9	8 central vesicle	4 macule	4 macule
10	7 central vesicle	3 macule	6 central vesicle
Mean	6.2±0.8	3.0±0.6	3.2±0.8

The numbers refer to diameter in mm. of area of injury. A dash indicates that no injury was detectable.

Methods: We used the second apparatus described above for producing a measurable and reproducible injury. With this, a skin area of 5 mm. diameter was heated within 15 seconds up to a temperature of 53.4 degrees C and kept at that temperature for one minute. With the exception of a few on the forearm all tests were made on the back.

Results and Discussion: In the first series the hormones were injected and the area stimulated immediately. As in the studies on the flare reaction, the immediate flare was inhibited by cortisone. However, the local injury became progressively greater at the cortisone site and after 5 days showed a marked delay in healing (see table 5, figure 1).

In the next series, the hormones were injected 5 hours after inducing the injury. After 5 days the cortisone area showed a marked delay in healing (see table 6). DCA showed indifferent reactions.

Then the hormones were injected first and the different areas were stimulated after 1, 2, and 3 hours respectively. Table 7 shows that both the inhibition of skin

flare and the delay of wound healing were marked at the site where the injury was made one hour after the injection of cortisone. There was a progressive decrease in these effects when the interval between the injection and the injury was prolonged (table 7, figure 2).

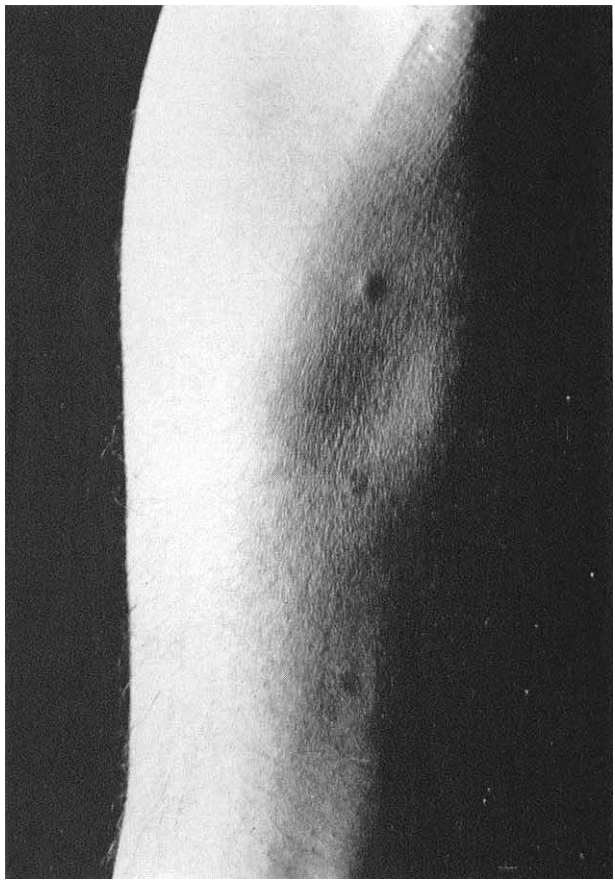

FIG. 1. The delay in wound healing with cortisone. All agents were injected locally immediately before injury. Photograph 5 days after injury.

To determine to what extent the observed effect was a true hormonal action we compared cortisone with saline, histamine, adrenaline and procaine. None of these latter substances showed an inhibiting effect like that of cortisone (table 8). In table 9 are the results of tests in which we compared cortisone with saline and supernatant fluid and found that the supernatant fluid was only slightly less active than cortisone, but this effect may be due to some cortisone remaining in the medium, especially since the latter was used undiluted. This impression was confirmed by the completely negative results with the use of the suspending

medium alone (table 9). Therefore, we think that the inhibition of healing by cortisone is a true local hormonal effect.

Histology: Biopsies were taken immediately after stimulation, 6 hours later and 62 hours later.

TABLE 6

Heat injury (53.4° C. for 1 min.) produced and 5 hours afterwards hormones injected. Area examined 5 days later

SUBJECT NO.	CORTISONE	SALINE	DCA
1	7 vesicle	6 vesicle	6 vesicle
2	7 scab	4 slight scab	3 macule
3	5 macule	—	—
4	6 macule	—	—
5	6 large vesicle	3 vesicle	3 vesicle
6	5 papule	—	—
7	5 vesicle	5 vesicle	4 vesicle
8	4 scab	25 macule	—
9	5 macule	5 slight macule	—
10	4 papule	—	—
Mean	5.4±0.4	2.6±0.8	1.6±0.5

The numbers refer to diameter in mm. of area of injury. A dash indicates that no injury was detectable.

TABLE 7

Area subjected to heat injury (53.4° C. for 1 min.) 1, 2, and 3 hours after substances injected (5 subjects)

	FLARE REACTION		AREA OF INJURY AFTER 5 DAYS	
	Cortisone	Saline	Cortisone	Saline
1 hr.	37.6 ±6.1	43.4 ±7.3	6.9 ±0.43	4.9 ±0.33
2 hrs.	39.8 ±5.3	47.6 ±7.3	5.0 ±0.41	3.8 ±0.65
3 hrs.	42.6 ±5.1	43.0 ±5.9	4.3 ±0.59	3.9 ±0.54

Numbers are diameters in mm. and the standard errors of the means.

In the "immediate" specimen there was less infiltration and more localization around the blood vessels and sweat glands in the cortisone slides. With the McMannus method the cells showed a deeper staining throughout with cortisone.

After 6 hours the effects of cortisone were hardly noticeable. The tissue appeared more compact and the collagen was mildly fragmented. These changes were absent in the saline injected skin. McMannus stain showed deeper staining with cortisone, but paling out of both sections compared with the "immediate" specimens.

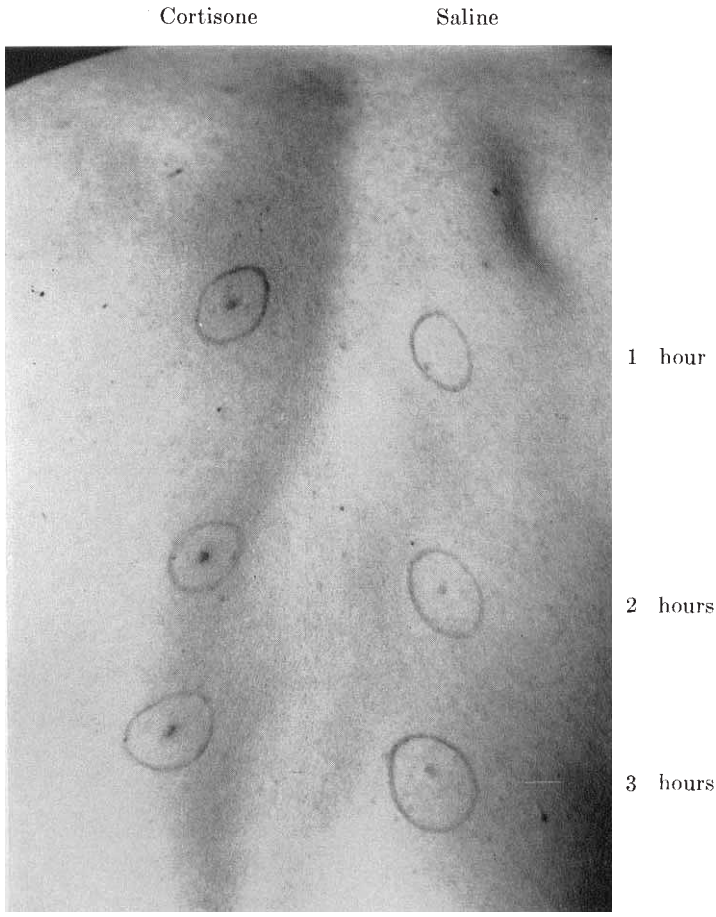

FIG. 2. The response to heat injury caused 1, 2, and 3 hours after the local injection of cortisone and saline.

TABLE 8

Effect of various agents on the flare reaction and on the rate of healing in response to local heat injury (53.4° C. for 1 min.) (5 subjects)

CORTISONE 5 MG./CC.	SALINE	EPINEPHRINE 1:1,000	HISTAMINE 1:100,000	PROCAINE 1%
Immediated Flare				
23.6 ±1.8	30.6 ±0.78	32.2 ±2.8	37.8 ±2.2	23.8 ±3.2
Residual Area of Injury (5 days)				
5.2 ±0.23	4 ±0.32	3.8 ±0.23	3.3 ±0.81	3.4 ±0.90

The numbers give the diameters in mm. and the standard errors of the means.

After 62 hours the saline slides showed hyperkeratosis and parakeratosis, fragmentation of the collagen of the papillary layer, localized infiltration of small round cells and moderate edema. With cortisone there was a sharply localized necrotic mass pushing through an epidermal rent. Both slides showed deep staining with the McMannus method, though again this was more pronounced in the cortisone section, where the stain of the necrotic mass was especially deep.

TABLE 9

The effect of pure cortisone powder suspended in saline and the commercial suspending medium and the supernatant fluid of cortisone on the healing process (6 subjects) residual injury at 5 days

PURE CORTISONE IN SALINE	SALINE	SUPERNATANT FLUID OF CORTISONE	SUSPENDING MEDIUM OF CORTISONE
4.7 ±0.3	2.0 ±0.8	4.0 ±0.6	1.7 ±1.0

Numbers are diameters in mm. and standard errors of the means.

THE EFFECT ON INTRADERMAL SPREADING

Review of Literature: In 1942, Cope, Breenizer and Polderman (6) found that in the dog the protein content of the cervical lymph was increased after adrenalectomy, and they considered this a proof of increased capillary permeability. During the last few years, with the increased availability of cortisone, this factor was examined from various approaches by a number of investigators. Seifter and coworkers (20) studied the influence of hyaluronidase and steroid hormones on the permeability of the synovial membrane. It was found that adreno-cortical extract decreased the permeability, while DCA had no influence. Opsahl published in 1949 a number of articles on experiments in the rabbit (17). She found that ACE inhibited spreading of dye in the skin, the effect being more pronounced with local than with intravenous administration. Adrenalectomy increased spreading, but this could be counteracted by ACE, though not by DCA. Compound A was less effective than compound E; testosterone, progesterone and pregnanolone had no effect. Winter and Flataker (26) found in experiments with mice and rats that cortisone and ACE inhibited spreading, but none of the other steroids tested had similar effects.

Regarding the effect on human subjects, Dorfman and Moses (9) reported that in rheumatic fever patients ACTH enhanced the hyaluronidase effect by neutralizing the nonspecific hyaluronidase inhibitor. This was confirmed by Hakanson and Luft (13). But Schmith and Faber (19) found the opposite effect, i.e., an antihyaluronidase effect of ACTH in the human serum. A possible connection between the delay of healing and the effect on spreading is pointed out by Videbaek (25) who thinks that the delaying effect of ACTH on healing may be due to disappearance of hyaluronic acid. Anderson and Wiesel (1) recently suggested that cortisone may retard spreading by inactivating sulfhydril groups. Benditt and coworkers (3) maintain that 24 hours pretreatment is necessary to obtain these effects and on this basis they believe that the effect is not a direct one. Ungar (24) actually isolated some substances from the spleen, which he considers the mediators between the pituitary-adrenal system and the observed peripheral effects.

Methods: In preliminary experiments on spreading, the hormones were injected as above, and after one hour 0.1 cc of a 2% solution of trypan blue was injected. When the interval between the injection of the dye and hormone was shortened, it was found that the effect on spreading became greater. Most pronounced effects were obtained when the dye was incorporated in the hormone

preparation, affording the added advantage of a reduced number of injections. This was the procedure for all tests reported here. Hyaluronidase (Alidase: G. D. Searle) 100 and 250 units per cc was added to the dye-hormone preparation and this increased the absolute amount of spreading in all cases. The distinc-

TABLE 10

The effect of the hormones on the intradermal spreading of trypan blue 2% (6 subjects)

SALINE AREA	CORTISONE AREA	DCA AREA
23 ±0.6	21 ±0.9	32 ±1.8

The numbers give the mean diameter of spreading 24 hours after the injection and the standard errors of the means.

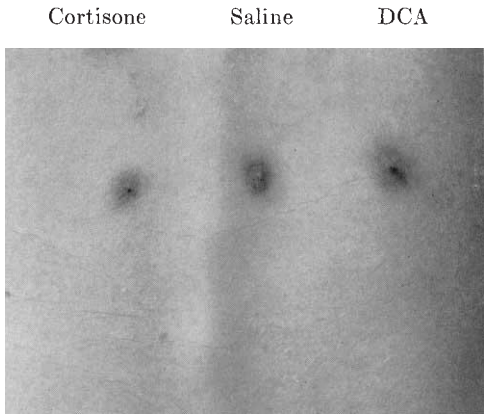

FIG. 3. Intradermal spreading of trypan blue. Relative inhibition with cortisone and enhancement with DCA.

TABLE 11

The effect of various substances on the intradermal spreading of trypan blue 2% (5 subjects)

CHOLESTEROL	ACE	CORTISONE	SUPERNATANT FLUID OF CORTISONE
28 ±0.78	22.4 ±0.71	21 ±0.95	26.4 ±0.95

The numbers give the diameter in mm. and the standard error of the means.

tive difference in spreading caused by cortisone and DCA remained nevertheless. Therefore, in subsequent experiments no hyaluronidase was added.

Results: Table 10 and figure 3 show that cortisone produced slight inhibition of spreading whereas DCA produced marked augmentation. While the DCA effect is very definite, we considered it desirable to further analyze the specificity of the cortisone effect. Therefore studies were done with cholesterol, adrenocortical extract and the supernatant fluid of cortisone suspension (table 11). In another series saline suspension of pure cortisone powder and the suspending

medium for commercial cortisone were used (table 12). The results of these studies confirmed the specificity of the action of cortisone as a spreading inhibitor.

TABLE 12

The effect of pure cortisone powder suspended in saline and the commercial suspending medium on intradermal spreading (6 subjects)

PURE CORTISONE	SALINE	SUSPENDING MEDIUM
16 ±0.8	24 ±0.8	23 ±0.6

The numbers give the mean diameters in mm. and the standard errors of the means.

SUMMARY

The local effects of intradermal injection of cortisone and desoxycorticosterone (DCA) in humans were determined in a large series of experiments. The results show:

1. Cortisone inhibits the immediate skin flare reaction produced by heat and various chemical agents, while DCA has no definte effect. This action of cortisone may not be a true hormonal effect.

2. In the majority of cases cortisone reduces the pain from local injury, while DCA is inert in this respect.

3. Neither of these steroids has any effect on the local sweating response produced by acetylcholine.

4. Wound healing is markedly delayed at the dermal site of injected cortisone, while DCA and saline have no effect.

5. Intradermal spreading of dye is markedly increased by DCA and slightly inhibited by cortisone.

A series of control experiments was performed to determine whether the effects observed are true hormonal actions or non-specific chemical effects.

DCA was kindly supplied by Ciba Pharmaceuticals, the pure "Cortone" powder and the vehicle for "Cortone" by Merck & Company.

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DISCUSSION

DR. LEON GOLDMAN, *Cincinnati:* I would like to ask Dr. Benjamin if he had any reaction to his intradermal cortisone?

In our work with local injections of cortisone now over one hundred patients, we have had a significant series of nodules from cortisone, and the biopsy shows among other things basophilic granular masses in the ground substance. And we have seen similar reactions also from deeper injections of cortisone with our Hypospray apparatus, and the question is, how much of this is due to cortisone and how much is due to the suspending agent which is not innocuous in its own right. The cortisone free suspending agent also caused some tissue damage but not nearly as much as cortisone material itself.

Now, even if we use a water soluble of ester cortisone, we still get some of this tissue reaction and it is quite surprising. In going over these results with Dr. Levine at Michael Reese, he wondered if our dosages of cortisone similar to what Dr. Benjamin used were not too excessive and actually we were getting toxic reaction from cortisone. We saw no local therapeutic effect from intradermal and deeper injections of cortisone locally in large series of patients, especially if they were well controlled and, incidentally, we were not able to inhibit any eczematous patch test reaction with intradermal cortisone or Hypospray cortisone locally. I would like to ask him if he noticed any of these reactions? We agree that there is no pain with the cortisone. In many instances we use no local anesthesia in the intradermal cortisone biopsy series.

DR. LIVINGOOD: I enjoyed this paper very much.

I get up here simply to corroborate what Dr. Goldman has said . . . and that is, to report a rather extensive experience with the use of cortisone locally in a rather wide variety of dermatoses with completely negative results including, in some cases, rather large doses of cortisone as high as 50 to 75 milligrams per gram in the ointment base. I am reasonably certain other people in the audience have had a similar experience.

DR. BENJAMIN: Naturally we were fully conscious of the conflicting clinical reports on the effect of local application of cortisone. In order to avoid the subjectivity of purely visual inspection we made biopsies 1) immediately after the injection, 2) after 6 hours, and 3) after 3 days.

In each case some slides were stained with hematoxylin-eosin and by the McMannus method. In the immediate response the cortisone area shows a more localized infiltration and deeper staining with McMannus than the saline comparison.

After 6 hours there is more fragmentation of collagen and again deeper staining with McMannus in the cortisone area.

After 3 days the saline area shows complete restitution while that with cortisone shows hyperkeratosis and parakeratosis and some necrosis in the corium.

All this may be a confirmation of the previous statement that the first reaction may be non-specific, while the delayed and spreading effect appears to be of a specific hormonal nature.