Influence of Cortisone upon Acute Inflammation.* (19273)

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Several workers have reported that the formation of granulation tissue is inhibited in animals treated with cortisone(1-5). This resulted in delayed healing of wounds. These findings suggested the desirability of determining whether cortisone retards the processes of acute inflammation. Accordingly a series of experiments was planned to secure evidence bearing upon this question.

Thermal injuries were chosen as the simplest form of uninfected lesions and best adapted to the purpose of these experiments. Such lesions were made upon the abdominal skin of guinea pigs weighing from 350 g to 400 g. In one series, burns were made by applying the mouth of a test tube, 8 mm in diameter filled with water at 90° to 95°C, to the skin for 10 seconds. In another series a pencil of solidified CO_2 (dry ice) about 6 mm in diameter was applied to the skin for 30 seconds. Such lesions were made in two groups of guinea pigs: one group treated with cortone®,† another group serving as controls. In each group, lesions of 24 hours, 6 hours, and 1 hour duration were made, after which the animals were killed under ether anesthesia and sections of the lesions were prepared for histologic study. Each of the treated guinea pigs received 2 injections of 5 mg cortone acetate intramuscularly on the day preceding the experiments and 2 such injections on the day of experiments. Twelve lesions each of 24 hours, 6 hours and 1 hour duration, respectively, were made by heat in cortone-treated animals, and the same number in untreated controls. Eight lesions of the same durations were made by freezing on cortone-treated animals and on 8 untreated controls. A total of 60 lesions in cortone-treated animals was compared with the same number of lesions made in untreated animals under identical experimental conditions.

Results. A prompt inflammatory reaction developed in all instances after the application of heat or cold. The latter provoked a milder reaction. Lesions of 1 hour duration consisted of hyperemia, slight edema and accumulation of leukocytes in the pre-capillaries, capillaries and venules. A few leukocytes were observed in the tissue spaces; diapedesis and occasional capillary hemorrhages were seen. These features progressed in degree and reached almost maximum intensity in 6 hours in the lesions made by freezing. There was further progression in the injuries made by heat.

Acute inflammation includes several major features, *i.e.*, hyperemia, diapedesis of red cells, capillary hemorrhages, edema and leukocytic infiltration, which vary in degree. It seemed appropriate to estimate the degree of each feature separately in each lesion examined. A marked degree of either feature was recorded as 3, a moderate degree as 2, a slight degree as 1, and absence of that feature was recorded as zero. While such a record of results is not mathematically precise, it provides a practical means for the required comparisons. Diapedesis and capillary hemorrhages were combined as one feature. Table I is a tabulation of results recorded by this method.

The sum of the figures in each column indicates the total degree of each feature in that group. By comparison, it is apparent that the degree of each item was less in the cortone-treated animals than in the untreated controls. This difference was greater in diapedesis plus hemorrhages and in edema than in the two other items. The results indicate also that the severity of the inflammatory reaction was greater after burns than after freezing, probably because the latter caused less severe damage to the tissues.

* Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinions or the policy of the Veterans Administration.

† Merck & Co. supplied cortone® used in these experiments.

TABLE I. Tabulation of Results.

Animal	24 hr				6 hr				1 hr			
	Hyperemia	Diapedesis	Edema	Infiltration	Hyperemia	Diapedesis	Edema	Infiltration	Hyperemia	Diapedesis	Edema	Infiltration
Burns: Cortone-treated												
23	2	0	1	1	2	1	1	2	1	0	1	1
24	3	3	2	1	3	3	1	3	2	1	0	0
28	3	3	1	1	3	2	1	1	2	0	0	1
29	3	3	1	0	2	2	1	2	2	1	1	0
35	2	1	2	1	3	1	0	1	3	0	1	0
38	3	3	2	2	2	1	2	2	2	0	1	1
39	2	2	1	2	2	1	2	2	1	0	1	1
42	3	3	1	1	3	1	1	2	2	1	1	1
51	2	0	0	1	2	2	2	1	2	0	1	1
52	2	1	1	1	2	2	2	2	2	1	1	1
53	1	0	3	3	2	1	2	2	1	1	1	0
57	2	0	3	1	1	0	3	1	2	1	3	1
Total	28	19	18	15	27	18	18	21	22	6	12	8
Burns: Untreated controls												
14	3	2	2	1	2	2	3	2	2	1	2	0
15	2	2	2	2	2	1	3	3	2	1	1	0
16	2	1	2	2	3	3	2	2	2	2	2	2
25	3	3	3	2	3	3	2	2	2	1	2	0
36	3	3	3	2	3	3	3	2	2	2	2	0
37	3	3	3	2	3	3	2	2	2	1	2	1
40	3	3	3	2	3	3	3	2	2	1	2	0
41	3	3	2	2	2	2	2	3	2	1	2	1
54	2	2	3	1	3	2	3	3	3	2	2	2
55	2	1	3	2	2	2	3	3	3	2	3	1
56	2	2	3	2	3	3	3	2	2	1	3	1
58	3	3	3	2	3	2	3	2	2	2	3	2
Total	32	28	32	22	32	29	32	28	26	17	26	10
Freezing: Cortone-treated												
20	1	0	1	1	2	0	1	1	0	0	0	0
21	1	0	1	2	0	0	0	0	0	0	0	0
26	2	0	2	2	0	0	0	0	0	0	0	0
27	2	0	2	2	0	0	1	2	0	0	0	0
30	1	0	1	1	0	0	2	2	0	0	1	0
31	0	0	1	1	1	0	2	2	0	0	1	1
35	2	2	1	3	2	1	2	2	2	0	2	1
42	1	0	2	2	1	0	3	3	1	0	1	1
Total	10	2	12	14	6	1	11	12	3	0	5	3
Freezing: Untreated controls												
19	1	0	2	3	1	0	3	3	1	0	1	0
22	1	1	2	3	2	0	3	3	1	0	3	3
32	1	1	3	3	2	0	3	3	1	0	2	2
33	1	0	3	3	2	0	3	3	2	0	2	1
36	2	1	2	3	3	1	3	3	2	0	2	1
37	3	3	3	3	2	0	3	3	2	0	2	1
72	2	1	1	3	2	1	2	2	1	0	1	1
73	1	0	1	1	1	0	2	1	1	1	2	1
Total	12	7	17	19	15	2	19	21	11	1	15	10

Physiologists have shown(6) that adrenal cortical steroids reduce capillary permeability or, in other words, they increase capillary resistance; hence it follows that under the influence of cortisone the passage of fluids from the blood into the tissues would be reduced, thus reducing the degree of edema. The same principle applies to diapedesis and capillary hemorrhages, assuming that capillary resistance is increased under the influence of cortisone. Benditt *et al.*(7) found that cortisone decreased the permeability of capillaries and lessened the spreading reaction which results from hyaluronidase. On the other hand, Menkin(8) reported that cortisone acetate injected intradermally caused an *increase* in capillary permeability. However, he intimated that this might be due to some substance present in the vehicle rather than to the cortisone itself. Michael and Whorton(9) recorded that the leukocytic infiltration, the formation of fibrin and the development of edema were strikingly altered in the early phases of acute inflammation in animals treated with cortisone. Robson and Duthie (10) cited the findings of other workers indicating that increased capillary resistance accompanies the "alarm reaction" in which cortical hormones are important factors. These observations were made following stress of various origins including heat, cold, ultraviolet light, x-radiation, nitrogen mustard, histamine, protein shock, insulin shock and others. These authors tested capillary resistance by applying a vacuum cup to an area of skin and determining the degree of negative pressure necessary to cause capillary hemorrhages in the skin. In cases of rheumatoid arthritis, spondylitis, lupus erythematosis and thrombocytopenic purpura under treatment with ACTH, they found that a definite increase in capillary resistance had occurred.

In view of these observations it is not strange that diapedesis, hemorrhages and edema after thermal injuries, were less in degree in animals which had received cortisone than in the controls. Increased capillary resistance may be a factor also in the degree of hyperemia resulting from tissue damage. The minute vessels may maintain their tonus and not dilate so readily or so extensively as under normal conditions. Furthermore, the walls of these minute vessels may offer more hindrance to the outward migration of leukocytes than would endothelium whose permeability had been increased. We noted frequently that leukocytes had congregated in large numbers within the lumina of the capil-

laries and venules, but relatively few had infiltrated the adjacent tissues.

Summary. (1) The inflammatory reactions resulting from thermal injuries were compared in cortisone-treated animals with those in untreated controls. (2) Diapedesis, capillary hemorrhages and edema were quantitatively much less in the cortisone-treated animals. Hyperemia and leukocytic infiltration also were less in degree but the difference in these items was not so marked as in diapedesis, hemorrhages and edema. (3) There is acceptable evidence that the corticoid hormones increase the resistance of capillary walls. The authors believe that this effect reduces the degree of each of the features in the inflammatory reaction.

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Received November 18, 1951. P.S.E.B.M., 1952, v79.

A Phenomenon of Topical Protection Against Hyperergic Inflammation by a Preceding Local Inflammation. (19274)

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The decrease in reactivity of living organisms in the course of repeated, non-physiological irritations or drug administration is a natural law of wide importance. One form of this is well known by the name of "tachyphylaxis." Following a similar principle, an anaphylactic reaction can be avoided by pretreatment of the sensitized animals with a small dose of antigen, whereafter the animals will tolerate a multiple of the lethal dose of antigen ("anti-anaphylaxis"). This phenomenon is mainly based on the exhaustion of specific antibodies in the tissues of the shock organs(1), and seems to be involved in desensitization. Furthermore, we know that protein therapy, which in itself has inflammatory properties, can also exhibit antiphlogistic effects—this being due to an endogenous discharge of gluco-corticoids through the mechanism of the "alarm-reaction"(2,3) and a consequent reduction of the "inflammatory potential"(4). In addition, the phenomenon of local immunity(5) has been shown by various investigators after a preceding nonspecific local inflammation. Thus, the spreading of topically injected virulent bacteria could

TABLE I. Topical Protection by a Preceding Inflammation Against Hyperergic Reaction. Six animals in each series.

Groups		1st inj., .2 ml, subcut.	2nd inj., 24 hr later, intraper.	Mean inhibition of inflammation in left hind paw, %
I	a	D (1:37.5)	E .5 ml (1:2.25)	97.2 ± 2.8
	b	D (1:37.5)	D 1 ml (1:37.5)	69.7 ± 2.8
II	a	E (1:5)	E .5 ml (1:2.25)	96.4 ± 1.6
	b	E (1:5)	D 1 ml (1:37.5)	100 ± 0
III	a	P (3%)	E .5 ml (1:2.25)	34.8 ± 6.3
	b	P (3%)	D 1 ml (1:37.5)	70.6 ± 9
IV		H (100 TRU)	D 1 ml (1:37.5)	68.8 ± 9

D = Dextran, E = Egg-white, P = Peptone, H = Hyaluronidase.