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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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.

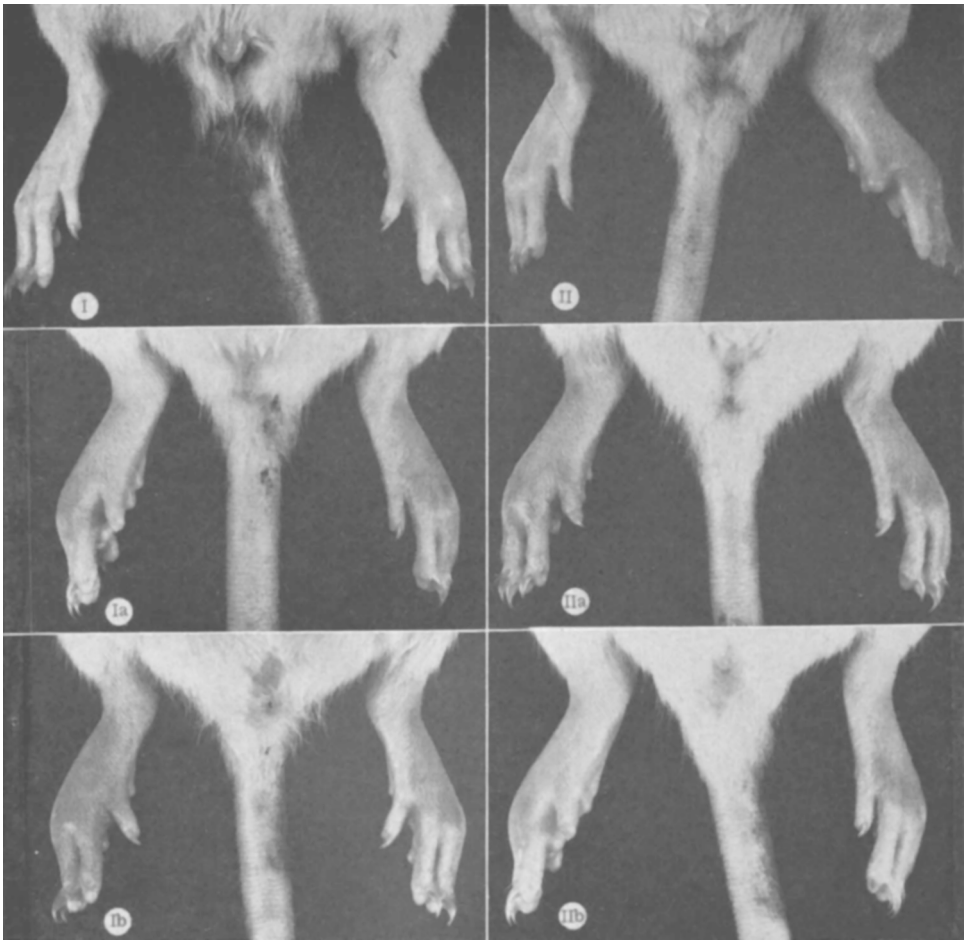

FIG. 1. Protection against dextran- and egg-white-induced hyperergic reaction by a preceding topical dextran or egg-white inflammation in left hind paw of the rat. I—Topical hyperergic reaction: .2 ml dextran (1:37.5) inj. subcut. into left paw (Group I). Ia—General hyperergic reaction 24 hr later: .5 ml egg-white (1:2.25) inj. i.p. (Group I) left paw protected. Ib—General hyperergic reaction 24 hr later: 1 ml dextran (1:37.5) inj. i.p. (Group I) left paw protected. II—Topical hyperergic reaction: .2 ml egg-white (1:5) inj. s.c. into the left paw (Group II). IIa—General hyperergic reaction 24 hr later: .5 ml egg-white (1:2.25) inj. i.p. (Group II) left paw protected. IIb—General hyperergic reaction 24 hr later: 1 ml dextran (1:37.5) inj. i.p. (Group II) left paw protected.

be prevented but also the spreading of color particles, probably by the formation of a fibrinous network (Menkin)(6). As far as we know, however, no studies have been undertaken to investigate the changes in the inflammatory reaction of tissues where nonspecific phlogistic agents are repeatedly administered.

Normally, inflammation proceeds in phases. In the acute phases a subsequent irritation can produce an additional effect. When gross evidence of inflammation subsides, however, we found an obvious resistance against the development of a new inflammation by further administration of an irritant. In the experiments, here described, we have paid special attention to the decrease or elimination of tissue reactivity which is not systemically but strictly locally conditioned.

Methods and results. Following an intravenous or intraperitoneal injection of egg-white(7) or of dextran(8,9) to rats, there develops a strong hyperemia and edema of the snout and paws, which lasts several hours.

A local inflammation of this kind can also be produced by injecting a small amount of egg-white(10) or of other similar agents directly into the paw. We prepared 42 male piebald rats (90-100 g) with a subcutaneous injection of 0.2 ml of various irritants, *i.e.*, dextran, egg-white, peptone and hyaluronidase into the aponeurosis of the left hind paw as shown in Table I. Twenty-four hours later, when the first reaction had disappeared, 6 animals of Groups I-III were given a second injection of dextran intraperitoneally, while the others of Groups I-III received an egg-white solution, also i.p. Another group of animals pre-treated with hyaluronidase received only dextran in the second injection (Table I). These intraperitoneal doses had been proven to produce an inflammatory reaction which was approximately 50% of the possible maximal reaction (9). Two, 3 and 4 fours after the second injection, the intensity of general inflammation was registered in the snout, front paws and right hind paw, and in the pre-treated left hind paw as well.

Depending on the intensity of the first topical reaction, the left paw showed a distinct protection against the action of the second injection, although the latter still produced a general anaphylactoid reaction (Fig. 1). It is pointed out that this protection phenomenon is non-specific. Dextran- and egg-white-induced hyperergic reaction can be inhibited topically by different phlogistic irritants. The preceding inflammation showed a decreasing degree of intensity after egg-white, dextran, hyaluronidase and peptone, in the order mentioned. This is probably why the topical peptone inflammation did not protect to the same extent as the other phlogistic agents, while the topical egg-white inflammation gave the greatest protection.

In order to obtain further data concerning this phenomenon, we studied the duration of the protection: 7 groups of 6 rats each (piebald, male, 90-100 g) were pre-treated with dextran (0.2 ml 1:37.5, injected subcutaneously into the left paw). After 6 hours, the topical inflammation had disappeared almost completely. A second injection of dextran (1.0 ml 1:37.5) was given i.p. as follows:

Groups	8 hr after first injection
I	
II	10
III	14
IV	22
V	38
VI	70
VII	134

The relatively long duration of the protection is shown in Fig. 2. Eight hours after the first injection, residual traces of inflammation in the left paw tended to augment the second inflammation and gave no inhibition. The protection became evident 10 hours after the first injection and increased to a maximum after 38 hours. The decrease of the protection proceeded slowly within the following 90-100 hours.

We are as yet unable to give a definite explanation for the mechanism of this "topical protection phenomenon," and we can only state that it is strictly locally-conditioned.

Summary. (1) The hyperemia and edema of an hyperergic reaction—induced by an intraperitoneal injection of dextran or egg-white in rats—can be topically inhibited by a preceding local inflammation. (2) The degree of this "topical protection phenomenon" depends on the intensity of the preceding inflammation. (3) The preceding inflammation was produced in the paw by a subcutaneous injection of small doses of dextran, egg-white, peptone or hyaluronidase. The phenomenon is therefore considered to be non-specific. (4) Under our experimental conditions the protection phenomenon reached its maximum 38 hours after induction of the first inflammation, and disappeared in the course of ap-

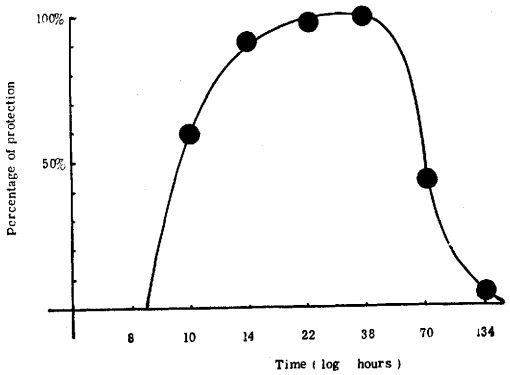

FIG. 2. Duration of protection.

proximately 5 days after the first inflammation.

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Effect of Anti-Rheumatic Drugs on Synovial Membrane Permeability.* (19275)

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Alterations in synovial membrane permeability have been described following the administration of various drugs. Seifter and co-workers(1) found that in rabbits hyaluronidase and desoxycorticosterone (DOCA) produced an increase in the rate of absorption and excretion of phenolsulfonphthalein (PSP) injected into the joint, and that Cortisone, ACTH, and an adrenal cortical extract inhibited absorption and excretion of the dye. They concluded from these studies that one of the controlling factors in membrane permeability is an antagonism between DOCA and Cortisone-like substances. In a later study(2), these investigators reporting on the effects of many steroid substances on synovial membrane permeability suggested that compounds impairing this permeability should produce an anti-rheumatic effect in patients.

Our study was designed to further evaluate the relationship between synovial permeability and the anti-rheumatic effect of cortisone and ACTH in animals and man. We undertook to explore synovial permeability by studying the rate of absorption and excretion of PSP following its injection into a joint. Since Seifter's studies had described its effective use, this appeared to be a convenient and accurate index. However, our results lead us to question the validity of this procedure as an accurate measure of synovial permeability.

Methods and materials. Studies on rabbits were conducted in male animals weighing 3 to 5 kg. Each animal was anesthetized with sodium amytal 100 mg/kg intramuscularly, and hydration was attained by the administration of 25 ml per kg of water by stomach tube. An indwelling catheter was secured in the bladder for collection of urine. PSP was injected into the ankle joint using 0.25 mg per kg, and after the injection, collections of urine were made by irrigation and manual expression of the bladder every 15 minutes for 2 hours. Urine samples were adjusted to a pH of 10.5 and diluted to a standard volume, filtered, and the optical density measured on a Coleman Junior Spectrophotometer at a wave length of 500 millimicrons. Excretion of the dye was calculated for each fifteen minute period as a percentage of the total dye injected. Cortisone was given to 7 rabbits for 11 courses in the doses shown in Fig. 1.

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