7013 C

Skin Changes after Subcutaneous Injection of Epinephrine.

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It is taught that epinephrine is much less effective by hypodermic or intramuscular injection than by the intravenous route. These differences are due to the rate of absorption, and this in turn to the vasoconstriction (Sollmann[1]). The unabsorbed epinephrine at the site of injection is apparently not destroyed, for the local blanching may persist from one to 8 hours (root of rabbit's ear, Auer and Meltzer,[2] Meltzer and Auer[3]; scarified skin, Sollmann and Pilcher[4]). When this epinephrine becomes gradually absorbed, it exerts its systemic actions. (Fornet,[5] Lyon[6]). It follows therefore, that if epinephrine were administered by a route such that it be slowly absorbed, its action would not be as sudden as by the intravenous route.

During an experiment in which epinephrine was injected subcutaneously in the rat, a considerable percentage of the animals showed skin changes at the site of injection, ranging from loss of hair to necrosis and, in a few cases, gangrene. As the experiment included the use of various doses, a record of the animals was kept with respect to size of the dose of epinephrine and degree of skin change.

The epinephrine was diluted with isotonic sodium chloride so that 1 cc. contained 0.4 mg. The full dose given was 0.1 mg. per 250 gm. of rat. In the case of the ½, ¼, ⅛ doses, the proper dilution was made. Abbott's epinephrine hydrochloride was used throughout the experiment.

Table I shows the relative changes with the various doses.

TABLE I

Dosage	No. animals	% showing only loss of hair	% showing breakdown of skin tissue	% showing no reaction
Full Dose	361	54	13	34
½ Dose	46	39	30	30
¼ Dose	169	5	0	95
⅛ Dose	30	—	—	100

[1] Sollmann, T., A Manual of Pharmacology, 437.

[2] Auer, J., and Meltzer, *J. Pharm. Exp. Therap.*, 1917, **9**, 358.

[3] Meltzer and Auer, *J. Pharm. Exp. Therap.*, 1921, **17**, 177.

[4] Sollmann and Pilcher, *J. Pharm. Exp. Therap.*, 1917, **9**, 309.

[5] Fornet, B., *Arch. f. exp. Path. u. Pharm.*, 1922, **92**, 165.

[6] Lyon, M., *J. Exp. Med.*, 1923, **38**, 655; *Quart. J. Med.*, 1923, **17**, 19.

The question arose as to whether these changes were due to the vasoconstrictor effect of the epinephrine or the acid which it contains. The acidity of our sample was determined by means of the hydrogen electrode. A solution of the corresponding strength of HCl was made and amounts equivalent to the quantities contained in the full dose of epinephrine were given subcutaneously. Forty-two rats were used. Twelve showed very slight hair loss but in no case, any signs of necrosis. It seemed, therefore, that the extensive skin effects were due to the epinephrine itself.

Patta[7] extracted the skin and subcutaneous tissue 2 hours after injection. He obtained a marked elevation of blood pressure upon intravenous injection of this extract, and concluded that epinephrine is not destroyed beneath the skin, at least within 2 hours. Luckhardt[8] injected, subcutaneously, 3 cc. of 1:1,000 epinephrine in the dog. Forty-nine pressor responses were obtained by the massage of this area. After 9½ hours, a saline extract was made from the subcutaneous tissue and a rise of 150 mm. of mercury was obtained as a result of its intravenous injection. He has obtained pressor effects from massage 19 hours after the subcutaneous injection of 1 cc. of 1:1,000 adrenalin HCl. Even after that time a saline extract of the subcutaneous tissue exerted, on intravenous injection, a marked pressor effect. He makes the significant statement that "the rate of absorption in the dog and in man must be different because in the dog, the subcutaneous injection of 1 cc. was followed in 19 hours by a moist gangrene of the injected area." Hare[9] states that he had seen cases where adrenalin had been given hypodermically and sloughs occurred.

We find that it is accepted by surgeons that such a skin effect may occur in man. At the Willard-Parker Hospital of New York City, instructions are given for massage of the injected area whenever itching recurs after the subcutaneous injection for serum sickness, etc. One injection will keep a patient comfortable from 12 to 15 hours.

Lederle Laboratoies issue a recommendation with their epinephrine for the massage of the injected area 24 to 48 hours after injection in order to obtain a second effect. Parke-Davis issues a similar recommendation.

In conclusion, it appears that epinephrine is not easily destroyed

[7] Patta, *Arch. d. Pharm.*, 1905, **4**, 329.

[8] Luckhardt, A. B., *Am. J. Physiol.*, 1927, **81**, 436.

[9] Hare, *Trans. Assn. Am. Phys.*, 1904, **19**, 233.

in the skin. It is probable that the tissues are sufficiently buffered to prevent the rapid decomposition of the drug.

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Growth Inhibiting Agent in Extracts of Desiccated Mammary Gland.

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Hormones, notably thyroxin, insulin, parathormone and epinephrine, have been shown to inhibit proliferation of the glandular tissues that produce them.[1, 2, 3, 4] The availability of these hormones in concentrated form made possible a determination of their effect on the mitotic rate of the glands. The histological methods for calculating rates of proliferation in the endocrine organs are equally applicable to tissues that do not produce internal secretions. In this laboratory aqueous extracts of desiccated kidney were found to inhibit the proliferation of the epithelium of the renal tubules when injected intraperitoneally into young rats.[5] Saline extracts of desic-

TABLE I

Mouse No.	CC. Ext. Injected	Mitoses per 10 mm.² 24 hrs. after injection	Mitoses per 10 mm.² at time of injection
1	1.2	505.5	772.3
2	1.4	244.0	387.5
3	2.2	58.5	271.8
4	2.0	4.1	345.3
5	2.4	60.6	66.4
6	2.2	250.6	1161.5
7	1.8	166.7	245.5
8	2.0	162.9	381.4
9	2.2	21.1	188.2
10	2.0	262.8	334.6
11	2.2	378.4	408.6
12	2.0	433.5	722.1
13	2.0	59.5	121.3
14	2.2	111.3	468.0

[1] Loeb, L., *J. Med. Res.*, 1920, **41**, 481.

[2] McJunkin, F. A., and Roberts, B. D., PROC. SOC. EXP. BIOL. AND MED., 1932, **29**, 893.

[3] McJunkin, F. A., Tweedy, W. R., and Breuhans, H. C., *Arch. Path.*, 1932, **14**, 649.

[4] McJunkin, F. A., Rall, R. R., and Singer, P. L., *Endocrinol.*, 1932, **16**, 635.

[5] McJunkin, F. A., and Hartman, C. D., *Am. J. Path.*, 1933, in press.