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Inhibition of the edema of paraphenylenediamine by drugs and relationship of the adrenals.

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In a previous study, the mechanism of edema formation in rabbits and cats receiving paraphenylenediamine was found to be concerned with a marked increase in vascular permeability, independently of nerve connections, in the head and neck regions[1] This report deals with a short summary of results on the nicotine inhibition, and certain other features.

The edema has been prevented in 70 per cent of 27 rabbits and cats by nicotine (5.6 to 26 mg. per kilo subcutaneously, or 1.4 to 14.7 mg. per kilo intravenously in divided doses). In the remainder, it has been retarded or not inhibited at all, for reasons which may be apparent from the results on adrenal relationship. The nicotine dosage employed did not cause paralysis of the sympathetic and parasympathetic ganglia. The inhibition was not concerned with the Gasserian ganglia and any hypothetical peripheral synapses in the edema organs, since the edema occurred after local infiltration with, and application of, nicotine, and also after degeneration of these structures. Nicotine did not inhibit the edema of the perfused head and extremities. Hence, the inhibition appeared to be systemic. It was not concerned with circulatory depression, for a high degree of circulatory efficiency was maintained throughout. Since the continuous intravenous injection of epinephrine and reduced blood flow to the head also inhibit the edema (Tainter and Hanzlik[1]), as does continued stimulation of the cervical sympathetic nerves (Gibbs), a similar mechanism, namely, vasoconstriction, resulting in reduced blood flow to the head, was suggested for the nicotine inhibition. This could occur through the adrenals, that is, by increased epinephrine output of these glands in virtue of the nicotine, a well-known action of this poison.

The dosage of nicotine used increased the output of epine-

[1] Tainter and Hanzlik, *J. Pharmacol. and Exper. Therap.*, 1924, xxiv, 179.

phrine as indicated by the cava pocket method of Stewart and Rogoff[2] in cats, and by the denervated and atropinized pupil of Meltzer[3] in cats and rabbits, the latter method being chiefly employed, and the pupillary response to epinephrine previously determined. Nicotine did not inhibit the edema in adrenalectomized cats, pupilo-dilatation being simultaneously absent. Pupilo-dilatation was marked during all inhibitions of edema in rabbits with adrenals intact, but it was absent in some rabbits that did not respond with nicotine inhibition, apparently due to inadequate output of epinephrine. Nicotine did not inhibit the edema in an ergotized cat whose sympathetic vasoconstrictors were unresponsive to epinephrine, as would be expected, even though ergot had not impaired the epinephrine output. However, in two rabbits with cut and supposedly degenerated sympathetic nerves, nicotine inhibition of the edema still occurred, apparently an inconsistency, providing the receptive substance on which epinephrine acts, was degenerated, but this was not ascertained. Of great importance was the fact that other drugs, which increased the epinephrine output of the adrenals like nicotine, namely, strychnine, picrotoxine and santonin, also inhibited the edema in the majority of rabbits, pupilo-dilatation occurring simultaneously in all those in which this was observed. Hence, these results were strictly consistent with the mechanism of the nicotine inhibition.

Thus, the edema of paraphenylenediamine was inhibited by essentially the same mechanism, the determining factor being presumably a decreased blood flow through the head and neck, however this might be brought about, whether by ligation of vessels, by sympathetic nerve stimulation, by injection of epinephrine, or by drugs which caused an increased output of epinephrine from the adrenals.

[2] Stewart and Rogoff, *J. Pharmacol. and Exper. Therap.*, 1916, viii, 479.

[3] Meltzer, *Am. J. Physiol.*, 1904, xi, 37.