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B 481 capillary resistance

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Lowered "Capillary Resistance" after iontophoresis of Lysergic Acid

Diethylamide

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THERE is some evidence that 5-hydroxytryptamine may be concerned in haemostasis (reviewed by Page¹); but it is difficult to test directly the haemostatic effect of the drug in normal persons, because, if it has such a role, it is presumably already available in optimal concentration. An attempt was therefore made to weaken the normal haemostatic system in man by treatment with lysergic acid diethylamide, which Gaddum, Hameed, Hathway and Stephens² have found to be a potent inhibitor of 5-hydroxytryptamine on the isolated rat uterus. Because of its effect on the personality, the drug could not be administered systemically. The effect of the drug was therefore investigated by measuring the 'capillary resistance' in small areas of skin which had been infiltrated by iontophoresis.

Solutions of lysergic acid diethylamide were prepared in 0.05 M phosphate buffer, pH 5.8-6.5 (depending on the solubility of the sample) at concentrations of 10^{-3} , 10^{-2} , 10^{-4} and 10^{-5} (calculated as base), and 0.4 ml. of a given solution was taken up in a thick blotting paper pad 2 sq. in. in area. This was placed on the skin of the anterior aspect of the arm and was made the anode of an iontophoresis circuit, following the method of Barcroft, Bonnar, Edholm and Effron³ with adrenaline. A current of 2 m.amp. was passed for 5 min. The pad was removed and haemostasis was tested by measuring the resistance of small vessels to reduced pressure⁴. After noting any existing petechiae, the total number of petechiae in the treated arm was successively recorded after reducing the pressure to 100, 150, 200, 250 and 300 mm. mercury below atmospheric. Each pressure was maintained for 30 sec. and the petechial counts were made after returning the test area to atmospheric pressure after each reduction. The symmetrically placed area of skin on the opposite arm was similarly tested after an identical treatment with buffer alone.

No personality changes were noted after these treatments, which suggests that only a small fraction of the drug contained in the pads entered the skin.

Thirty-one series of petechial counts were thus obtained from both arms (the right arm was treated with the drug in twelve tests and the left arm in nineteen tests) in four subjects (three male and one female). The effect of treatment was investigated as follows. For each arm, the petechial count was plotted against the negative pressure, and the count corresponding to - 275 mm. mercury was estimated by linear interpolation. The pressure required to give, on the opposite arm, the lower of these counts was then estimated in the same way. The difference

between these pressures was taken as the response; a positive sign was attached if the higher count at - 275 mm. mercury occurred with lysergic acid diethylamide, or a negative sign if with buffer alone.

The mean responses differed significantly from zero only at the two higher doses, being (with standard error) 56.5 ± 26.3 (ten responses; $P = 0.04$) at a dose of 1/1,000, and 100.5 ± 26.3 (ten responses; $P = 0.001$) at 1/100. The slope of the regression of response on logarithm of the dose of lysergic acid diethylamide was also significant ($P = 0.01$) over all the responses. There was no evidence of a systematic difference between the responses from the two arms, from the different sites, from different subjects or from different days of testing; although the number of petechiae appearing in the untreated skin at a given site exposed to a given fall in pressure clearly varied from subject to subject, and was higher at proximal than at distal sites.

This method of calculating the response was particularly influenced by the high counts obtained at the extreme negative pressures. Two alternative methods of calculating a response, which gave less weight to the extreme pressures, yielded similar results with regressions significant at $P = 0.06$ and 0.08.

It may thus be inferred that, after this treatment with lysergic acid diethylamide at 1/100, and perhaps at 1/1,000, a larger number of petechiae were produced at a given site by a given fall in pressure than would otherwise have been expected. Nevertheless, in a small series of tests in one subject, no increase in bleeding time was obtained after the iontophoresis of lysergic acid diethylamide into the nail beds of the fingers: the bleeding time was measured in test and control areas under microscopic observation¹.

The present experiments therefore suggest that 5-hydroxytryptamine may at least be concerned in preserving the integrity of undivided small vessels: that is, in preventing the occurrence of purpura.

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¹ Page, I. H., *Physiol. Rev.*, 34, 563 (1954).

² Gaddum, J. H., Hameed, K. A., Hathway, D. E., and Stephens, F. F., *Quart. J. Exp. Physiol.*, 40, 49 (1955).

³ Barcroft, H., Bonnar, W. McK., Edholm, O. G., and Effron, A. S., *J. Physiol.*, 102, 21 (1943).

⁴ Scarborough, H., *Edin. Med. J.*, 48, 555 (1941).

⁵ Macfarlane, R. G., *Quart. J. Med.*, 34, 1 (1941).