Histamine and 5-Hydroxytryptamine Content of Tissues after Prolonged Treatment with Polymyxin B

SIR,—Bushby and Green[1] in 1955 were the first to show that polymyxin B releases histamine in rats and this antibiotic was later used by Parratt and West[2] to produce a maximal depletion of histamine from some rat tissues. These latter authors gave five doses intraperitoneally over three days and, in addition to obtaining a depletion of histamine from some tissues, recorded a loss of 5-hydroxytryptamine but this was restricted to the inner layers of the skin and the pads of the feet. This dose schedule has been extensively used in the past two years to deplete the skin of its histamine without altering its 5-hydroxytryptamine concentration. We have now found that, when the treatment with polymyxin B is continued for a longer period than three days, there is a reduction in the skin 5-hydroxytryptamine content and a further loss of histamine from tissues other than the skin.

TABLE I

COMPARISON OF THE DOSES (MG./KG.) OF POLYMYXIN B USED IN THE PRESENT WORK (TREATMENT A) WITH THOSE USED BY PARRATT AND WEST (TREATMENT B)

Day of treatment	Treatment A	Treatment B
1	1	2·5
2	2·5, 2·5	5, 5
3	5, 5	7·5, 7·5
4	7·5, 7·5	—
5	7·5, 7·5	—
6	10	—
7	10, 10	—
Total dose of polymyxin B	76	27·5

Female albino rats (180–190 g.) were injected with polymyxin B according to the dose schedule shown in Table I and killed 24 hours later. Extracts of tissues both rich in mast cells (e.g. skin) and deficient in mast cells (e.g. jejunum and pyloric stomach) were then assayed for histamine and 5-hydroxytryptamine as previously described.[3] The results are compared in Table II with those of previous authors[2] who used fewer doses of polymyxin B. The histamine levels in the jejunum and pyloric stomach of those rats receiving 12 doses (treatment A) were found to be considerably lower than those of rats receiving 5 doses (treatment B). Whereas the 5-hydroxytryptamine content of the jejunum and pyloric stomach is only slightly reduced, that of the skin tissues (abdominal skin, ears and feet skin) is markedly lowered, the average reduction being 44 per cent.

TABLE II

THE HISTAMINE AND 5-HYDROXYTRYPTAMINE CONTENTS OF SOME TISSUES OF RATS RECEIVING DIFFERENT TREATMENTS OF POLYMYXIN B, AS SHOWN IN TABLE I. ALL VALUES ARE EXPRESSED AS PERCENTAGES OF THE CONTROL LEVELS

	Histamine		5-Hydroxytryptamine	
	Treatment A	Treatment B	Treatment A	Treatment B
Feet skin	5	6	46	83
Ears	8	4	65	102
Abdominal skin	23	8	56	73
Pyloric stomach	33	75	72	95
Jejunum	41	60	83	95

It is important, therefore, to choose a suitable dose schedule of polymyxin B for the preferential depletion of tissue histamine in the rat, for prolonged treatment reduces the 5-hydroxytryptamine content of tissues as well as that of histamine. Other potent histamine liberators such as compound 48/80[2,4,5] also release both histamine and 5-hydroxytryptamine, but whilst the release of 5-hydroxytryptamine by compound 48/80 usually precedes that of histamine, with polymyxin B the reverse occurs.

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The Determination of Meprobamate as the Dixanthyl Derivative

SIR,—Roth and others[1] have characterised meprobamate (2,2-di(carbamoyloxymethyl) pentane) by means of its dixanthyl derivative and report only a melting point of 182°. Algeri and others[2] also used the dixanthyl derivative to identify meprobamate, but give no constants for their derivative. We obtained a higher melting point product, by dissolving meprobamate and xanthenol in glacial acetic acid and allowing the solution to stand for 10 hours or more at room temperature[3]. After recrystallisation from hot methanol and drying to constant weight, the nitrogen content of the crystals, which melted at 188° to 189°, was found to be 4·80 per cent. This value agrees with the calculated value of 4·84 per cent for a product of molecular weight 518·42 derived from the reaction of 2 moles of xanthenol and 1 mole of meprobamate.

The spectral absorbance of dixanthyl meprobamate in various solvents showed two maxima at 240 and 289 mμ similar to those shown by solutions of 9-xanthenol. An E (1 per cent, 1 cm.) (λ289 mμ) of 142·5 was found for solutions of the dixanthyl derivative in methanol, ethanol and isopropanol, and was used to calculate the solubility of the compound in saturated solutions of the various solvents shown in Table I.

The best yields of dixanthyl meprobamate were obtained by reacting 0·100 g. of meprobamate with 0·3 g. of 9-xanthenol in 5 ml. of glacial acetic acid, and seeding with 5 to 10 μg. of dixanthyl meprobamate crystals. After standing for 16 hours, 45 ml. of 80 per cent aqueous isopropanol was added to the reaction flasks and the solutions refrigerated for 1 hour. The crystals were transferred to a tared sintered glass filter with 15 ml. of the aqueous isopropanol and dried to constant weight at 100°. The weight of the crystals multiplied by 0·3769 gives