group at C-14 although epimerization of this latter group was previously considered to destroy such activity.

*Departments of Anaesthetics and Clinical Measurement, Westminster Medical School, Westminster Hospital, London, S.W.*1, *England.*

J. M. LEIGH

Pharmax Ltd., Thames Road, Crayford, Kent, England.

A. D. S. CALDWELL

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Cobalt ion action on the vascular permeability and mast cells of the rat

The action of cobalt ion has been reported to be similar to that of histamine (Niebroj, 1958). Recent evidence suggested that only the second phase of cobalt-induced diphasic change in the vascular permeability of the guinea-pig skin was accompanied by local necrosis (Steele & Wilhelm, 1967). The present report supplies additional evidence on the mechanism of action of the metal on the vascular permeability and on the mast cells.

Male Wistar rats anaesthetized with urethane (600 mg/kg intraperitoneally) were used. $CoCl_2.6H_2O$ (AR) and histamine phosphate solutions were made up with saline (0·85%). The water used for solutions was previously deionized. Intradermal injections of 0·005, 0·01 and 0·02 M of cobalt chloride (pH 6·0) and 4·0 and 8·0 μg of histamine were made and control intradermal injections with 0·1 ml saline. The conventional technique for study of the vascular permeability using a 1% azovan (Merck) blue solution was used (Rocha e Silva & Dragstedt, 1941; Miles & Miles, 1952). In some of the animals promethazine hydrochloride (1 mg/kg) was previously injected intravenously. The cobalt ion effect on the morphology of the mast cells of the mesentery was assessed using a technique described to us by I. Mota (unpublished). This procedure allows microscopic observation of the mast cells of the mesentery *in situ* fixed and stained. 1 ml of a 0·02 M cobalt chloride solution was intraperitoneally injected. After 20, 40, 60 and 80 min, and under light ether anaesthesia, 10 ml of a 0·5% acetic acid, 10% formalin and 0·5% toluidine blue solution was intraperitoneally injected. After 2 h, small fragments of the mesentery were collected, washed in distilled water, attached to a slide and dried at ambiental temperature.

At the concentrations used, cobalt ion induced an immediate increase in the vascular permeability of the rat skin similar to that provoked by histamine. The strongest colour intensity provoked by the metal was always weaker than that elicited by histamine. Promethazine hydrochloride completely prevented the effect of histamine but not that of the cation. The microscopic examination of the mesentery showed that the morphological aspects of the mast cells were not altered by the cation.

Three alternative hypotheses may be formulated to explain the cobalt effect on the vascular permeability: the first, that the effect arose from the hydrogen ion concentration of the unbuffered solution of the salt; the second, an indirect mode of action mediated through the local liberation of histamine; and the third, a direct action of the metal. The first hypothesis seems unlikely since it was demonstrated that pH influences vascular permeability only when it is markedly acid or alkaline (Opie, 1963). Again, the effect does not seem to be mediated through a local histamine liberation, since the action was not inhibited when an antihistamine agent was previously injected and there was demonstrably a lack of action of the metal on the mast cells of the mesentery. The third, and as yet unexplained effect of cobalt in increasing vascular permeability by a direct action of the metal, must now be elucidated.

Department of Pathology
and Department of Pharmacology,
Faculty of Veterinary Medicine,
University of São Paulo,
São Paulo, Brazil.

M. MARIANO
B. MARIA DE LOURDES
S. DE MORAES
J. PALERMO NETO

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Dissolution characteristics of reserpine-polyvinylpyrrolidone co-precipitates

This is a report of a preliminary investigation made to ascertain the dissolution characteristics of a relatively water-insoluble drug reserpine in the form of a co-precipitate or solid dispersion with polyvinylpyrrolidone (PVP). The use of solid dispersions or co-precipitates to facilitate dissolution has been previously reported (Sekiguchi & Obi, 1961; Gibaldi; Feldman & Bates, 1968 & workers there cited; Decato, Malone & others, 1969; Stoll, Bates Nieforth & Swarbrick, to be published).

Reserpine–PVP solid dispersions, in ratios of 1:3 and 1:6, were prepared by dissolving both components in reagent grade chloroform and subsequently removing the solvent by vacuum evaporation. The co-precipitates were dried *in vacuo* to constant weight, screened through standard mesh screens and the 40 to 50-mesh (297–420 μm) fraction collected for use in the dissolution rate studies. Pure reserpine (6–30μm crystals) and a 1:3 reserpine–PVP physical mixture (6–30 μm crystals used) were also subjected to dissolution rate testing.

The dissolution apparatus consisted of a 500 ml three neck round bottom flask containing 350 ml of a 0·005M acetic acid solution (pH 3·65) maintained at 37° $\pm$ 0·1°. The solution was agitated at 60 rev/min by a Teflon stir blade of 70mm diam. connected to a Servodyne-constant torque motor assembly. At time zero, a quantity of reserpine equivalent to 10 mg was introduced into the medium. Periodically 5 ml samples were removed from the flask, subjected to Millipore filtration (0·45 μm pore size) and assayed for drug content using a Beckman DB-G recording spectrophotometer. Reserpine in acetic acid obeys Beer's law at a wavelength of 268 nm. Following the removal of each sample, a 5 ml quantity of fresh dissolution medium was pipetted