microscopy or the Coulter Counter are often used, the microscope being more suitable for drugs such as salbutamol which have high solubility in polar solvents.

The microscope method (based on B.S. 3406 Part 4, 1963) is slow and errors tend to occur due to operator fatigue and the small number of particles measured.

The speed and accuracy of measurement are increased considerably by using the microscope in conjunction with an image analysing computer—we have used a Quantimet 720 (Metals Research Ltd; Fisher & Cole, 1968). Salbutamol is dispersed ultrasonically in a suitable oily dispersant containing surfactant and is then examined on microscope slides. The Quantimet measures the maximum horizontal chord (i.e. scanning in one direction) of each particle and the particles are automatically classified into eight pre-set size classes.

The retained samples from eighteen production batches of micronized salbutamol were measured in duplicate with the Quantimet. The size distributions on every batch are log normal and give similar slopes on a log probability graph. The mean slope (i.e. standard deviation) is 1·59 and the mean particle size by weight (d_{gw}) is 2·00 μm diameter (range 1·52–2·44 μm). On average about 70% of the particles by weight are between 1 and 3 μm.

The excellent uniformity between the batches is illustrated by the low standard deviation (0·20 μm) and the small range (1·52–2·44 μm) in d_{gw}.

The results illustrate the excellent reproducibility of the micronizing process and the suitability of particle size of the micronized drug for use in inhalation aerosols. Clearly the Quantimet 720 is suitable for accurate sizing of fine isodiametric drug particles.

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Disposition of disodium cromoglycate administered in three particle sizes

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A recent investigation showed that small particles of disodium cromoglycate (DSCG) exert, in asthmatic patients, a protective effect which is dramatically greater than that of large particles (Godfrey, Zeidifard & others, 1974). Another recent investigation showed that the response to, and urinary excretion of, DSCG are related (Benson, Curry & others, 1973). DSCG is assayed in urine by purification on Amberlite resin and coupling with p-nitroaniline to give a coloured solution which is assessed spectrophotometrically (Moss, Jones & others, 1971; Curry & Mills, 1973). We now report the results of an investigation of the disposition of DSCG inhaled in particles of three sizes by 5 volunteers.

Doses were inhaled in random order during three attendances at weekly intervals. DSCG was drawn from a spinning disc generator (described earlier) (Godfrey, Zeidifard & others, 1974). Each subject provided a set of urine samples at each attendance, consisting of a pretreatment sample and samples at 0·5 or 1-hourly intervals up to 5 h after the dose. Additionally, each subject provided a set of mouthwash samples, collected at a fixed time after completion of dosing, and any DSCG exhaled during dosing was collected in a filter. Particle sizes were (as median diameter): small, 2·0 μm; intermediate 6·0 μm; large 11·7 μm. The standard deviation on these readings was 1·1 to 1·4 in several experiments. Mean doses were: small, 940 $\pm$ 23·4 (s.e.m.) μg; intermediate, 1244 $\pm$ 105·7; large, 1016 $\pm$ 29·7. Mean urinary retrieval was: small, 34·9 $\pm$ 10·0 (s.e.m.) % of dose; intermediate 13·6 $\pm$ 6·0; large 13·9 $\pm$ 4·5. Mean retrieval in mouthwashes was: small, 5·2 $\pm$ 2·1; intermediate 7·8 $\pm$ 3·3; large 46·0 $\pm$ 20·0. Mean exhaled material was: small, 2·2 $\pm$ 0·7 (s.e.m.) % of dose; intermediate 2·1 $\pm$ 1·0; large 2·3 $\pm$ 1·3.

Thus urinary retrieval was highest from small particles, while mouthwash retrieval was highest from large particles. Exhaled material was unimportant. Material untraced was presumed to have been swallowed and excreted in faeces, and/or absorbed and excreted in bile. The small particles will have penetrated most easily to the most distant parts of the bronchial tree, so this study and those quoted earlier, give added weight to the belief that the action, and transfer of DSCG across the pulmonary epithelium into the blood stream, both occur most favourably in the smallest airways. Additionally, it can be concluded the DSCG would be best administered as small particles, since large particles were deposited to a great extent in the mouth.

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The effects of some prostaglandins on respiration in the rabbit

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Certain prostaglandins have been shown to stimulate respiration in various animal species; the dog, calf, rat, guinea-pig, and man (Maxwell, 1967; Lewis & Eyre, 1972; McQueen, 1972, 1973 and references cited therein). Excluding man, all studies involved animals anaesthetised with pentobarbitone sodium.

This report records our findings during preliminary investigations into the influence of some naturally occurring prostaglandins and their derivatives on both the normal and depressed respiration of New Zealand White rabbits. From three to six rabbits were used for each study. Animals (adult, of either sex and body weight 3·5–4·0 kg) were anaesthetized with halothane and used as such, or dosed with a solution of one of 19 barbiturates (up to 400 mg), including thiopentone and Brietal sodium, 7 narcotic analgesics (up to 5·5 mg), urethane (up to 2·5 g), chloralose, or glutethimide (both up to 500 mg), until a standard number of respirations min^{-1} was obtained, and the mean femoral arterial blood pressure allowed to regain a steady value. The drug solutions were administered by slow infusion via a marginal ear vein during which time the anaesthetic was increasingly diluted until totally replaced by room air. Insulation and spot lamps were used to maintain the normal body temperature of the rabbits to within $\pm 1°$. Prostaglandins (PGs) were administered i.v. or i.a. via femoral or marginal ear vein, or common carotid artery, in normal saline or in dimethylacetamide (DMA) diluted 0·3:100 with normal saline, and respiration, tidal volume, blood pressure and ecg monitored. DMA alone in normal saline (up to 10% v/v) did not influence any of the parameters monitored.

All PGs excluding 16, 16-diMe$PGF_2\alpha$ elicited an increase of up to 10× the resting respiratory rate and respiratory minute volume in animals dosed with pentobarbitone sodium. PGE_1, PGE_2 and $PGF_2\alpha$ also elicited a rise in respiratory rate in the animals receiving other barbiturates, and $PGF_2\alpha$ elicited a comparable rise in all other animals except those receiving dihydrocodeine, diamorphine and glutethimide. Respiratory stimulation was enhanced most by 15(S)15-MePGE_2Me ester, followed in order of decreasing potency by 15(S)15-Me$PGF_2\alpha$Me ester, 15(S)15-Me$PGF_2\alpha$, PGE_1, 8-iso PGE_2,PGE_2, $PGF_2\beta$ $PGF_2\alpha$, $PGF_1\beta$, PGA_1, PGA_2, $PGF_1\alpha$, PGB_1, PGB_2, 5,6-trans $PGF_2\alpha$, 20-Et$PGF_2\alpha$, 8-iso $PGF_2\alpha$. Doses, equivalent in effect, ranged from 5 nanomoles for 15(S)15-MePGE_2Me ester to 1 micromole for 8-iso $PGF_2\alpha$. The tidal volume was not significantly influenced by any prostaglandin. Compared with the other prostaglandins tested, the F series was as much as 5× longer (1·25 to 2 min) in effecting a maximum response. Defaecation was observed