treatment of the cns manifestations of lead toxicity will, of course, depend on additional factors. For example, because of the differential absorption, binding and intracellular uptake of these compounds (see Chisolm, 1968), it is possible that the *in vivo* reactivation of brain adenylate cyclase may differ somewhat from that seen *in vitro*. Nonetheless, the procedure outlined here offers a rapid, convenient and physiologically meaningful assay for the initial screening of potentially effective chelating agents for use in the treatment of cns lead toxicity.

March 28, 1977

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The segregation of granules during tableting

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In the manufacture of tablets segregation of dissimilar granules can occur during the flow of granules from the hopper and also within the hopper as a consequence of vibration. As the drug content of granules of differing size can vary significantly (Lachman & Sylwestrowicz, 1964; Selkirk, 1976), segregation of granules could therefore contribute to variations in the drug content of tablets. To investigate this variation a series of batches of granules have been made from blends of two size fractions of lactose granules. One part of each blend contained the dye eosin so that variation in the ratio of granules from each size fraction, in the final tablet, could be studied.

Preparation of granules. A number of 2 kg batches of granules were prepared using a conventional massing and screening technique. The binder was 5% w/w solution of polyvinylpyrrolidone (220 cm^3) with or without eosin (1·0 g). The damp mass was forced through a 1·0 mm sieve dried at 60° in trays in an oven fitted with a fan and rescreened through a 1·0 mm sieve using a Jackson-Crockatt granulator. The dried granules were sieved into 5 size fraction >1·0 mm; 1·0 mm–710 μm (fraction A); 710–500 μm (fraction B); 500–250 μm (fraction C) and <250 μm. The sieve fractions from each batch were combined to give sufficient granules in each size fraction for the subsequent tableting experiments.

Assay of granules. Fractions A, B and C were assayed for eosin content, 5·0 g of granules were dissolved and made up to 500 cm^3 with water. The resulting solutions were assayed colorimetrically, the eosin contents were 0·490, 0·508 and 0·501% for batches A, B and C respectively.

Preparation of tablets. The tablets were prepared from 500 g batches of granules lubricated with 0·5% sodium lauryl sulphate (and 0·5% magnesium stearate if necessary) using a Manesty E3 machine. Each batch except one consisted of a 50:50 blend of two size

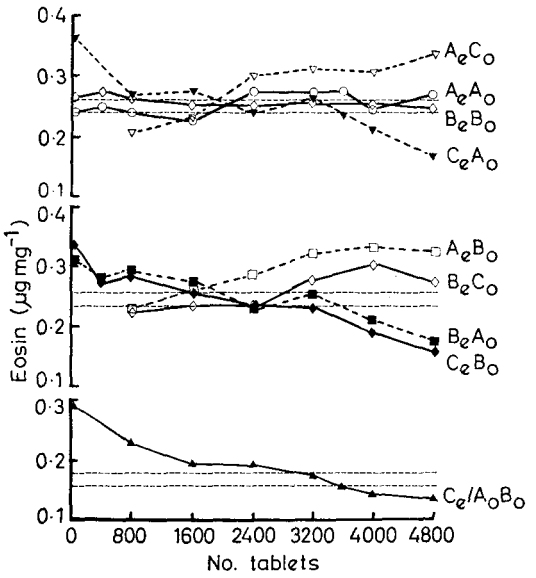

FIG. 1. Variation in eosin content of tablets with number of tablets produced during a single tableting run. The dotted lines indicate the significance limits ($P = 0.95$) for tablets containing the theoretical mean quantity of eosin.

A granule—1·0–710 μm subscript e eosin. B granule—700–500 μm subscript o no eosin. C granule—500–250 μm.

fractions, one of which contained eosin, this gave a 100 mg tablet that contained approximately 25 μg eosin. The granules were mixed by hand to visual homogeneity and then layered in small (approx. 25 g) aliquots into the hopper to minimize segregation during this stage. The compression weight was set to about 100 mg and the granules were converted to tablets (¼″ flat) in a single run at 72 min^{-1}, the compression weight was adjusted if necessary while the tablets were being made to maintain a constant value throughout the run. The first 40 tablets were collected and a further 40 were collected after 400, 800, 1600, 2400, 3200, 3600 and 4400 tablets had been made. The total yield between was 4500 and 4800 tablets. The tablets in each sample were individually weighed and assayed colorimetrically for eosin content; solutions containing magnesium stearate were filtered using a Swinnex millipore filter (0·8 μm) before assay. The results are summarized in Fig. 1. Each point represents the mean of 40 tablets from a single run. The first results indicated wide variations at the beginning of each run and therefore analysis of the 1–40 and 400–440 tablets was omitted from the later batches.

The limits indicated in the figure by dotted lines are the $P = 0.95$ limits for eosin content mg^{-1} around the mean of 0·25 μg mg^{-1} corrected for granule potency. The sample to sample variation in coefficient of variation of the eosin content mg^{-1} was not significant ($P = 0.95$). The dotted lines therefore represent the variation about the theoretical mean 0·250 μg mg^{-1} for (a) and (b) or 0·167 μg mg^{-1} for (c) 2·02 × (mean standard deviation) for batches of 40 tablets.

The variability of the tablets weights decreased with decreasing granule size but otherwise remained at a similar value throughout compression of any batch. Values or coefficient of variation were (eosin fraction indicated by the first letter) AA 2·10, AB 1·00, BA 1·00, AC 1·13, CA 0·98, BC 0·60, CB 0·72, BB 0·88, C(AB) 1·11%. From Fig. 1 it can be seen that segregation resulted in the 4000–4040 and 4400–4440 either having an excess of a deficiency of eosin. This corresponded to a deficiency of the finer granule, which has separated in the hopper and hence has been incorporated into the earlier tablets to a greater extent. When the granules are of a similar size range segregation does not occur, tablets (AA and BB). Whether the granule size fractions are adjacent (AB, BC) or not (AC), makes no significant difference to the extent of segregation during tableting. A mixture of equal weights of the three size fractions studied C(AB) showed a pattern of segregation similar to that found for binary mixtures. It would therefore be reasonable to assume that when there are significant variations in the drug content with granule size then granule segregation will produce batches of tablets with a dose dependent upon the amount of tablets previously compressed. This variation will be greatest at the beginning and end of each tableting run.

March 10, 1977

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