Table 3. Results of Rank Sum Test of significance for disintegration times obtained with two different meshes, A and B. A difference significant at the α level exists if the parameter $M_\alpha > R$ the Rank Sum.

No. of measurements with mesh A, n_2	= 105
No. of measurements with mesh B, n_1	= 95
Rank Sum Coefficient R	= 8549
$M_{0.10}$	= 8877
$M_{0.05}$	= 8746
$M_{0.01}$	= 8493

report will remain valid and will still be relevant to the new test.

Conclusions

Only one of the two meshes in use on disintegration testers was found to comply with the B.P. specification. As a result of comparisons carried out with a batch of sugar coated tablets, it was shown that there was a difference between the disintegration times significant at the 0·05 level. The difference in the mean values was 15% which underlines the importance of ensuring that the mesh sizes comply with the B.P. specifications.

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Influence of pimozide on the locomotor hyperactivity produced by caffeine

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Methylxanthines are known to produce various effects on the amount and turnover of putative neurotransmitters within the brain, e.g. release and enhanced turnover of noradrenaline (Berkowitz et al 1970; Waldeck 1971), increase or decrease of dopamine turnover (Corrodi et al 1972; Waldeck 1971, 1973, 1975) and decreased turnover leading to enhanced concentrations of 5-hydroxytryptamine (5-HT) (Berkowitz & Spector 1971; Corrodi et al 1972; Valzelli & Bernasconi 1973). Interactions of methylxanthines with dopa (Strömberg & Waldeck 1973) and acetylcholine (Waldeck 1974, 1975) have been also reported (for review see Eichler 1976; Waldeck 1975). Considering the diversity of these findings it is difficult to correlate any of the data with the behavioural effects of caffeine and thus to try to elucidate the basic mode of action of the drugs. Experiments from our laboratory revealed that in mice the caffeine-induced locomotor stimulation could be markedly reduced by *p*-chlorophenylalanine, a depletor of brain 5-HT, while the α- and β-adrenoceptor-blocking agents phenoxybenzamine and propranolol were ineffective in this respect (Estler 1973). On the other hand, Waldeck (1973) reported an inhibitory effect of pimozide, a dopamine antagonist, on the caffeine-produced motor excitation. Since Waldeck's (1973) results, obtained only with a high dose of pimozide and according to Andén et al (1970) might have produced unspecific effects, seemed to contradict our own findings, I have reinvestigated the effect of pimozide on the caffeine-induced motor stimulation using different doses of both drugs.

Adult male mice were kept at 25° C (room temp.) with free access to a standard diet (Herilan) and tap water. They were injected s.c. with caffeine sodium benzoate at amounts corresponding to 25 or 50 μg of the free base per g weight. Some of the animals were pretreated with 0·3 or 1·0 $\mu g\ g^{-1}$ pimozide s.c. 4 h before the administration of caffeine. Mice treated only with the same doses of pimozide or with saline served as controls. The number of animals in each treatment group ranged from 20–28. Measurements of locomotor activity of single animals were made according to Estler & Ammon (1969). The observation period was 2 h starting either immediately after the injection of caffeine or saline, respectively, or 4 h after the injection of pimozide.

Saline-treated mice placed into the activity cages showed an initial phase of increased motility (orientational hypermotility) during the first half hour. Afterwards the activity declined to a constantly low level (resting activity) (Fig. 1C). Caffeine increased the orientational and resting locomotor activity, 50 $\mu g\ g^{-1}$ being more effective than 25 $\mu g\ g^{-1}$ (Fig. 1A, B). Pimozide when given alone at a dose of 0·3 $\mu g\ g^{-1}$ did not affect the orientational and resting motility, pimozide 1 $\mu g\ g^{-1}$ depressed the orientational hypermotility but had no effect on the resting activity (Fig. 1C). When mice pretreated with pimozide 1 $\mu g\ g^{-1}$ were injected with caffeine 25 or 50 $\mu g\ g^{-1}$ 4 h later, caffeine completely lost its stimulatory effect. The lower dose of pimozide (0·3 $\mu g\ g^{-1}$) abolished the effect of the lower dose of caffeine (25 $\mu g\ g^{-1}$) but did not diminish the motor stimulation produced by 50 $\mu g\ g^{-1}$ caffeine (Fig. 1A, B).

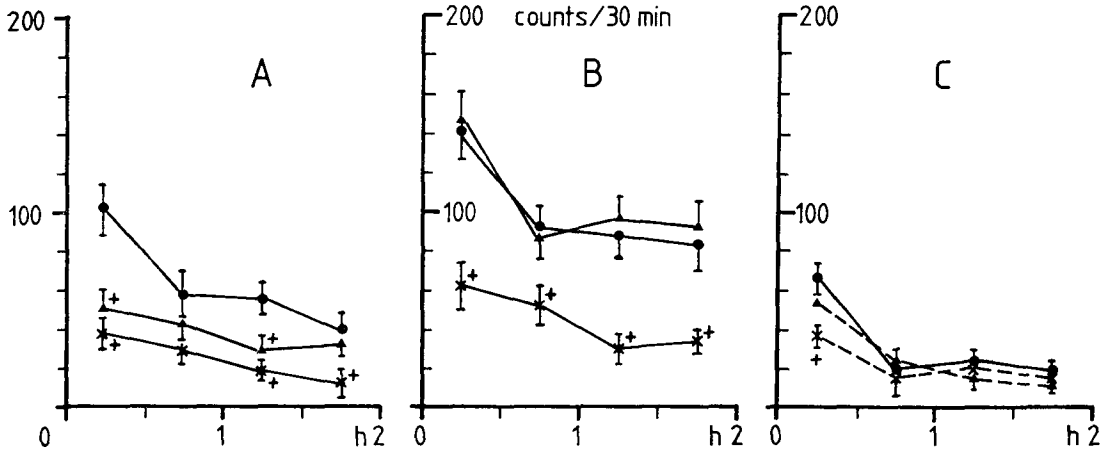

FIG. 1. Locomotor activity of mice treated with caffeine and pimozide. Mean values ± s.e.m., N = 20–28. A. ●——● Caffeine (25 μg g^{-1}, s.c.), ▲——▲ pimozide (0·3 μg g^{-1}, s.c.) + caffeine (25 μg g^{-1}, s.c. 4 h later), X——X pimozide (1·0 μg g^{-1}, s.c.) + caffeine (25 μg g^{-1}, s.c. 4 h later). * P vs caffeine alone ⩽0·05. B. ●——● Caffeine (50 μg g^{-1}, s.c.), ▲——▲ pimozide (0·3 μg g^{-1}, s.c.) + caffeine (50 μg g^{-1}, s.c. 4 h later), X——X pimozide (1·0 μg g^{-1}, s.c.) + caffeine (50 μg g^{-1}, s.c. 4 h later). * P vs caffeine alone ⩽0·05. C. ●——● Saline, ▲— —▲ pimozide (0·3 μg g^{-1} s.c., 4 h previously), X— —X pimozide (1·0 μg g^{-1}, s.c., 4 h previously). * P vs saline ⩽0·05. Ordinate: counts per 30 min. Abscissa: time (h).

The observation that pimozide at a dose of 1 μg g^{-1} completely abolished the stimulatory action of caffeine confirms the earlier observation by Waldeck (1973). However, this finding alone does not provide convincing evidence for a dopaminergic mode of action of caffeine, since the effect may be unspecific because: (i) According to Andén et al (1970) pimozide, at doses exceeding 0·5 μg g^{-1}, in addition to its antidopaminergic properties also exhibits effects on noradrenaline turnover; (ii) the fact that, as in the experiments by Waldeck (1973), pimozide 1 μg g^{-1} also depresses the hypermotility of untreated mice suggests that at this dose pimozide may act through its neuroleptic and tranquillizing properperproperties, unless one presupposes that orientational hypermotility is also dopaminergic in origin. The finding that the lower dose of pimozide, which is thought to specifically block dopamine receptors within the c.n.s. (Janssen et al 1968a, b), effectively depresses the stimulatory action of caffeine, 25 μg g^{-1} supports more conclusively the hypothesis of Waldeck (1975) that the central stimulation produced by caffeine is caused by a dopaminergic mechanism. But this assumption becomes questionable again if one takes into consideration that pimozide 0·3 μg g^{-1} has no effect against the stimulating effect of the higher dose of caffeine, which, on the other hand can be blocked by p-chlorophenylalanine (Estler 1973).

Therefore, it appears that a dopaminergic action alone cannot account for the caffeine-induced central stimulation. Most probably psychostimulation by caffeine is a complex phenomenon in which several neutrotransmitters are involved, as is also suggested by data by Corrodi et al (1972). In this context it is interesting that Grabowska (1976) & Maj et al (1975) have provided evidence for an interaction between the dopaminergic and the serotoninergic system of the c.n.s.

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