The self-inhibiting effect of acetanilide on the formation of methaemoglobin

SIR,—It has been reported that as the homologous series of anilides (acetanilide to dodecylanilide) was ascended, the ability of the compounds (orally, 1 mmole/kg) to induce the formation of methaemoglobin in cats was at a maximum at propionanilide and n-butyranilide (McLean, Murphy & others, 1967a) (see Fig. 1). If, however, the same series of compounds was administered at a dose of 0·5 mmole/kg and all other experimental procedures used were as described by McLean & others (1967a) a different pattern of results was obtained (Fig. 1A). In the second case the ability of the compounds to induce the formation of methaemoglobin fell regularly as the homologous series was ascended. The problem arises as to why this difference in response should occur.

If acetanilide is considered, it may be seen from Fig. 1 that a dose of 1·0 mmlole/kg produces less methaemoglobin than 0·5 mmole/kg and it is the only anilide which does this. A log dose response curve of acetanilide (oral) and aniline (i.v.) is shown in Fig. 2. From this it can be seen that at lower doses there is a linear relationship between log dose and the mean percent methaemoglobin formed with acetanilide, but at higher doses this relationship does not hold. Aniline given intravenously also shows a linear log dose response curve over the same range of mean percent methaemoglobin formed.

When aniline was administered to cats which had previously been anaesthetized, the amount of methaemoglobin produced was less than that in control animals given the same dose of aniline (McLean, Robinson & others, 1967b). This reduction in the response was shown to be independent of the nature of the anaesthetic used or the route by which it was administered. Further, it was also established that this "anaesthetic effect" was due to the metabolism of aniline to phenylhydroxylamine (the proximal methaemoglobin forming compound) being modified rather than the effect of phenylhydroxylamine on the enzyme systems of the red blood cell being affected.

It is well known that the structurally non-specific biological depressants such

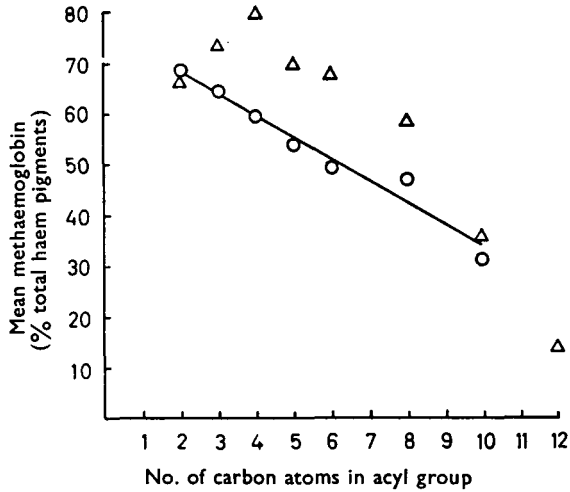

FIG. 1. Methaemoglobin formed by anilides. Each point is the mean value from either 4 or 6 cats. The value for each cat is the mean of the hourly readings of % methaemoglobin for 6 hr following the administration of each compound. The anilides were administered orally at dose levels 1·0 mmole/kg (6 cats each) △, and 0·5 mmole/kg (4 cats each) ○—○.

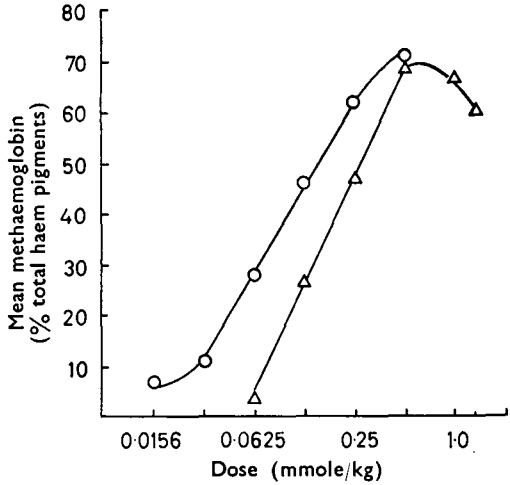

FIG. 2. Log dose response curves for aniline (i.v.) ○—○ and acetanilide (oral) △—△. Each point is the mean value from 5 cats. The value for each cat is the mean of the hourly readings of % methaemoglobin for 5 hr after the administration of aniline and 6 hr after acetanilide.

as the general anaesthetics depress the activity of many biological activities other than central nervous activity and it is not surprising, therefore, that the rate of *N*-hydroxylation was reduced by such a compound. Acetanilide in high doses has a central depressant effect and appears to act as a structurally non-specific depressant. A possible explanation of why the pattern of results obtained at 1 mmole/kg was different from the pattern obtained at 0·5 mmole/kg with the series of anilides (Fig. 1) is that acetanilide inhibited its own metabolism to phenylhydroxylamine by its structurally non-specific depressant action. However, it has been reported that acetanilide at a dose of 0·75 mmole/kg was a potent inhibitor of the metabolism of methanol in mice (Hassan, Elghamry & Abdel-Hamid, 1967). The mechanism of this action was said to be unknown but since the metabolism of ethanol was not inhibited by acetanilide the authors suggested that this action of acetanilide was due to a specific mechanism. This was thought to be due to acetanilide causing a depletion of the peroxide pool of the body. If this is so then it offers another explanation why acetanilide has a self inhibiting effect on its ability to induce the formation of methaemoglobin.

Acknowledgements. One of us (S.M.) wishes to thank the Pharmaceutical Society of New South Wales S.E. Wright Research Trust for a Research Grant.

Department of Pharmacy,
Department of Pharmacology,
University of Sydney,
Sydney, N.S.W., Australia.

J. THOMAS
S. MCLEAN
G. STARMER

August 31, 1967

References

Hassan, A., Elghamry, M. I. & Abdel-Hamid, F. M. (1967). *Can. J. Physiol. Pharmac.*, **45**, 291–298.

McLean, S., Murphy, B. P., Starmer, G. A. & Thomas, J. (1967a). *J. Pharm. Pharmac.*, **19**, 146–154.

McLean, S., Robinson, J., Starmer, G. A. & Thomas, J. (1967b). *Ibid.*, **19**, 803-809.