FROM: M J Godley

MJG/KH

TO: Dr L L Smith

cc Mrs A Fenna
Dr B Woollen
Dr I F H Purchase
Dr S E Jaggers

25th September 1984

COMMENTS ON DRAFT DOCUMENT ENTITLED 'EFFECT OF THE ADDITION OF AN EMETIC TO PARAQUAT FORMULATIONS ON ACUTE POISONING IN MAN' BY T B HART & A WHITEHEAD

1. There are several cases of apparent differences in 'total' counts of cases. Undoubtedly this is often due to not all the information being available in all cases to enable inclusion in all tables by various factors. However, I feel some comment to this effect might allay fears that the numbers are 'incorrect'. Others may be the result of my misunderstanding the figures in which case perhaps more comprehensive table headings would resolve, eg:

   a) pg 5 para 2 '230 cases' comparted to pg 6 Table 2 with a total of 224 cases.

   b) Does Table 3 refer to solid and liquid formulation or solid only? Pg 8 line 8 says all cases but total in Table 3 is 218 and in Table 4 145 + 110 = 255.

   c) Pg 1 para 2 '640 cases' compared to a total of 783 in Table 4.

2. Has the balance of solid to liquid formulation changed (Tables 1 and 2)?
   'Non-emetic' (older) cases solid 181 liquid 146 (ratio 1.2:1)
   'Emetic' (newer) cases solid 160 liquid 64 (ratio 2.5:1)
   Is the identification of formulation containing emetic 'easier' if solid rather than liquid?

3. Table titles 1 and 2 'poisonings' compared to 'formulations'.

4. Should second lowest dose category in Table 3 read '2 to <5g' (not '3 to <5g') as in Table 4? This would correspond with text statement on pg 8 line 6 'doses of 2 to 5g ... associated with about 50% mortality'.

5. I have checked by crude methods the numerical support for some of the statements made ie

   a) Pg 5 last para: 12% and 64% being 'lower' than 21.5% and 84% - justified.

   b) Pg 9 1st para: 44% reduction 'greater' than 24% reduction - justified.

   c) Pg 8 para 3: increased incidence of vomiting 67/69 compared to 45/60 - justified.

6. The paper acknowledges that a number of other factors may influence the mortality data (pg 8 and 9). The references to 'treatment for paraquat poisoning' and possible differences pre-1974, made me interested to know the years applying to the two data bases 'emetic' and 'non-emetic'. The conclusion that differences in 'treatment for paraquat poisoning' are unlikely to be an influencing factor on mortality rates is a little strong. In the case of liquid formulations it is undoubtedly reasonable to assume that this factor could not 'explain' the reduced mortality but in the cases of solid formulations even though 73% of the 'non-emeticised' group occurred after 1974 it is possible (by applying a 47% mortality rate pre-1974 and a 12% mortality rate post-1974 - for both emetic and non-emetic groups)- for the reduced mortality rates observed to have been totally the result of 'improved' treatment.

7. The phrase 'potential lethal dose' is unclear to me. It is not quantitatively defined and appears on pg 8 para 1 to be more related to the incidence of 50% mortality ('2 to 5g ... associated with about 50% mortality') than to what I intuitively expected, ie the lowest dose at with lethality becames a real possibility. I have difficulty reconciling the statement that 'the potentially lethal dose to man is between 2 and 5 g ...' (pg 8 line 8) when Table 3 clearly shows deaths at doses of <2g. (I acknowledge the uncertainties associated with the dose estimates in this Table.) The implication of the observation that following the introduction of the emetic the potentially lethal dose is '... rather more than a mouseful ...' (pg 8 line 4 para 2), ie that a mouthful is <u>not</u> potentially lethal, seems unconvincing to me.

8. Finally I am concerned about the way in which the data in Table 3 might be abused.

   For example assuming dose levels for each category of <2g (say 0.5g), 2g to <5g (say 4g) and 5g to <10g (say 8g) the application of a probit mortality dose-response relationship yields estimates of the human LD50 of 2.8g but more importantly of an LD1% (intuitively a 'potential lethal dose'?) of 0.14g.

I believe the data cannot 'prove' reduced mortality due to the emetic but on balance a reasonable judgement would be that it has made some contribution to this.

M J GODLEY