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Dear Gerry,

Following are some comments on the ACNP task force notes of 6th February, 1973 regarding both the general considerations and the proposal for evaluating antidepressant drugs. My comments may also be relevant to the notes by Uhlenhuth and Wittenborn.

1. Distinction of phase of study

While the general statements elicit approval and little criticism, I am confused by the mission. Guidelines for testing safety are different from guidelines for efficacy. There are necessary differences in rules for phase I and dosefinding studies by experienced clinicians from rules for phase III general clinical surveys by an army of technicians, and phase IV clinical trials by hosts of practitioners.

As I read the general considerations, these seem focussed on phase II-III studies - verification of efficacy in small samples by technicians. What of the special issues of

(a) identifying clinical populations (phase I)

(b) dosage measurement

(c) physiological effects including toxicity?

In the guidelines, the selection of depressed patients is scored as a symptom, a complex, and a disease, and resolves the dilemma by approving all these. I believe these distinctions to be important, and while the identification of homogeneous populations for phase III-IV studies is a difficult chore, it is one that needs emphasis. These distinctions are even more important in phase I trials, where heterogeneous populations should be encouraged, and the data presented not as statistical "salamis" but as case records,

focussed on the interrelation of symptom, syndrome, or disease and intervention. (The case studies by Klein make a unique contribution in this regard, and support for such studies is warranted). Again, the distinction of goals of each study dictates distinction as to methods, and I suggest that the guidelines focus on different "phases" with different guidelines. (For another opinion, see Hollister [enclosed]).

2. Distinction of dosage

Differences in observations, particularly as to efficacy, are related not only to the target symptom and population selected, but delivery of adequate doses of the agent to target organs. Reports of wide differences in blood levels with thymoleptics and lithium, when patients are given the same dosages, has led to speculation about genetic differences in metabolism affecting therapeutic results. While genetic and metabolic differences may indeed operate, the intake, absorption, and the influence of feeding dosage are simpler, more mechanical issues that require study. As with the utility of blood lithium, and blood DPH levels, perhaps the recommendations should include comments that where physiologic indices exist, therapeutic studies should include concurrent dosage-index measures: at a minimum, daily (or more frequent) urine and blood levels; and, as frequent heart rate, EKG, or cerebral bioelectric measures where these may reflect tissue levels. Cerebral bioelectric measures, reflecting the effect of an agent on a target organ most directly in antidepressant therapy, are the best index of changes in cerebral activity, and have wider applications than the guidelines reflect. (Cerebral potential [EEG] studies also allow an identification and classification of antidepressant, thymoleptic, and euphoriant drugs, providing a guideline as to the related comparison treatment).

3. Measures of toxicity

To gain some acceptance of a new antidepressant, only to find it to have some cardiotoxicity or to affect the lens of the eye, would serve society little. I have been concerned by the neglect of cardiac toxicity in early evaluations, for example, with thioridazine and mesoridazine. An evaluation that does not contrast a profit-cost accounting is a poor evaluation: to estimate efficacy is limited if it does not contrast with the established, "effective" standard. Thus, the guidelines may suggest that change scores of behavioral measures should be evaluated in the same set as changes in blood, cardiac, cerebral, etc. indices. (i.e. after items 1 and 2 [page 4], there should be an assessment of "secondary" effects).

(In this regard, items 4, 5, 6, 7 are clearly post-evaluation indices, useful to the technicians and clinical researchers, but not relevant to evaluation in phase~~III~~II efficacy and safety).

There is a particular problem in assessing antidepressants: the "standard" is not well accepted, for imipramine and amitriptyline, MAO, and ECT are each quoted by different evaluators for different purposes. For a "major" antidepressant, it may have to be contrasted with ECT. For the others, with imipramine. The guidelines might suggest when to use which contrast, and perhaps discard any continued use of MAO inhibitors as a standard.

The separation of phase of study and heterogeneous, case studies for phase I; emphasis on homogeneous populations for phase II, III; distinctions of dosage and physiologic indices; and cost-profit analyses for toxic symptoms are questions that are also lacking in the anti-anxiety guidelines. The notes by Wittenborn reflect an interest in a very late phase of clinical testing, and yet he attempts to approach the relevant issues. As I read his notes, his emphasis is on phase III, large scale testing - he notes the frequent difficulty in dosage, washout, etc. that are also relevant to the issue of antidepressants.

Perhaps the guidelines are only focussed on phase III-IV testing as Wittenborn suggests; then these notes are inappropriate. Perhaps phase I trials require different guidelines, and such a separation of goal may be useful in separating and clarifying the guidelines. Should you or the Committee wish an elaboration of these thoughts, I will try to amplify them with more specific suggestions.

Sincerely yours,

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Enc.
cc. T. R. Wittenborn, Ph.D.