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The Editorial Board of this JOURNAL *has established the policy that where there is an interesting and sharp difference of opinion between an author and a reviewer, if it appeared to be more valuable to publish a statement of the differences than to attempt to make one of the disputants agree with the other, this would be done with the permission of both parties. In this way interesting as well as educational material which would otherwise be lost is published. The publication of a reviewer's commentary should make his contribution a more substantial one, to the reader as well as to the author. It is for this reason that we publish a commentary on Dr. Berger's paper and leave it to the reader to come to his own conclusions. Editor.*

Commentary on preceding article

The author should be congratulated for bringing together a large number of pertinent and diversified references dealing with his chosen subject. There is no question in my mind that meprobamate differs in some respects from barbiturates. One can compare chemical structures, physical and chemical properties, and finally pharmacologic actions and show many differences as well as similarities. The same sort of statement, however, can be made for pentobarbital versus phenobarbital. Depending upon one's objective, the differences or the similarities can be emphasized.

My principal objection to the manuscript is that the title would suggest that the similarities as well as the differences between meprobamate and barbiturates will be discussed equally. The manuscript clearly is biased toward the differences, frequently being noncritical of the reputed differences, and very critical of the similarities. As a result, the manuscript provides excellent copy for drug advertisements but little scientific objectivity. As discoverer of meprobamate, the author is so close to it that it is difficult, if not impossible, for him to be completely objective in discussing his highly successful "offspring."

The following are specific points which I would like to comment on.

Page 209, paragraph 2. The author refers to his own publications classifying meprobamate as a "central relaxant." Surely, he has had personal experience with cocktails and can attest to the

fact that ethyl alcohol in proper dose would fit his definition of a "central relaxant." In fact, the author should have discussed meprobamate in relation to ethyl alcohol as well.

Page 209, paragraph 3. After creating a new classification for meprobamate to differentiate it from the phenothiazines, the author refers to the barbiturates as sedative hypnotics which of course they are. However, they can also be used as "central relaxants." I would disagree with the statement, "Barbiturates resemble one another very closely. . . ." Phenobarbital has a selective motor depressant effect that clearly is not present with pentobarbital, etc. Amobarbital has a euphorogenic effect not present with barbital, etc. It is, therefore, not correct to say that the differences between barbiturates are quantitative. He should not use the word barbiturates so indiscriminately but refer to specific ones more frequently.

Page 210, column 1, lines 6-10. The author implies that "barbiturates" and meprobamate have a single site of action which is different. These agents have many sites of action. Frequently the two classes of drugs have similar sites of action (for example, depression of the hippocampus) but differ quantitatively. They have similar clinical applications in many situations.

Page 210, column 1, lines 20-29. The author should specify in detail the effects of a large variety of barbiturates for there are appreciable differences in the amount of excitation with each. The statement, "After meprobamate, animals rested peacefully. . . ." could apply to phenobarbital in proper dose.

Page 210, column 1, lines 36-43. The statement that the reticular activating system is the site of action of sedative hypnotics refers to a relatively old article which does not give all of the presently known facts. It is therefore entirely inadequate and inappropriate. For example, there is good evidence that very low doses of barbiturates depress the hypothalamus, cortex, and limbic system.

Page 210, section "effects on the reticular activity system." This section is markedly oversimplified, especially in the light of research in the past few years. The activating system includes medullary as well as hypothalamic components in addition to the midbrain. The diffuse thalamic projection system is more involved with sleep than arousal, especially when recruiting responses are elicited. The statement "so-called arousal" for low voltage, fast frequency activity is not as critical as it should be inasmuch as the same activity is seen during dreaming and low doses of meprobamate and certain barbiturates. The reference to Magoun that sedatives block this response in nonhypnotic doses lacks the qualification of level of stimulation with regard to threshold.

Page 210. Table I serves no useful purpose in its present form for the 1:4 ratio of pentobarbital and meprobamate assumes parallel slopes of the dose-response curves. The author might argue that human doses are also in a 1:4 ratio. However, in all probability meprobamate has a much shallower dose response curve. Therefore, much larger doses of meprobamate or smaller doses of pentobarbital should have been used for the comparison. This is critical with respect to much of the research in animals that the author subsequently reviews.

Page 211, first column. The author should try to explain the discrepancies between the data of Gangloff (more stimulation of reticular formation) and Takaori and Ohato (no effect or depression of reticular formation) or conclude that Gangloff's findings were not confirmed. In fact Gangloff confuses the issue by not differentiating fast waves of activation from fast waves of depression as in the case of barbiturate or meprobamate fast waves. The author makes a strong point of the differences between meprobamate and barbiturates as per Gangloff, and does not equally emphasize the similarities of barbiturates and meprobamate as per Takaori and Ohato.

Page 211, paragraph beginning "The effect of meprobamate." This summary paragraph should point out that all of the previous studies referred to did not include thorough dose-response curve data and that many of the reported differences between some barbiturates and meprobamate may be related to this.

Page 212, column 2, paragraph 1. In criticizing the research of Shagass and co-workers, the author fails to appreciate the importance of tolerance development to meprobamate. This is why the dose can be increased to such large levels and still be relatively ineffectual clinically.

Page 214, column 1, paragraph 2. The author should emphasize more the work of Abdulian and co-workers pointing out the similarities of meprobamate to pentobarbital rather than to mephenesin and SKF 1045. The author fails to refer to the work of King and others that small doses of pentobarbital block the polysynaptic reflexes selectively just like mephenesin. Important articles such as that of Pfeiffer and associates are referred to primarily in order to emphasize the differences rather than the similarities of meprobamate to other sedatives.

Page 217, Table II. Should it not refer to only those differences that are statistically significant? Why are comparisons of parameters in which the differences are not statistically significant included? The table in its present form gives the impression of far more differences than are statistically verified. Dose relationships should include even smaller doses of secobarbital.

Page 218, column 1, paragraph 2, line 11, sentence, "This is not surprising as the drug was

given at four times. . . ." The point is that large doses can depress these functions like any other sedative in large doses. Therefore, in this respect meprobamate does resemble a sedative.

Page 218, column 1, paragraph 3. The important point of quantitative rather than qualitative differences to other sedatives is not stressed.

Page 218, column 2, paragraph 1. The author gives the wrong impression of the work of Pfeiffer and associates on conditioned reflexes. Meprobamate does not have a selective effect on avoidance behavior, just like a barbiturate. He fails to quote Hertz as well as other workers on this point.

Page 219, column 2, paragraph 1. The research of Hughes and co-workers should have been criticized on the basis of the doses of the various drugs used. Therefore, their tranquilizer indexes are meaningless.

Page 220, column 1, paragraph 1. The first sentence is quite objectionable because it implies barbiturates are ineffective in psychoneurotics. The real point is that meprobamate came at a time when physicians were overly concerned with the hazards of addiction to barbiturates and were ready for something described by a catch phrase as a so-called "nonaddicting tranquilizing muscle relaxant without autonomic nervous systems effects," etc.

Page 224, first paragraph. The "infrequent" use of meprobamate may be related to the less frequent therapeutic use of meprobamate than barbiturates.

Page 224, last half of first column. The discussion should be modified in accordance with some of the above comments.

Page 224, second half of second column through first column of page 225. The criticisms of Laties and Weiss conclusions should include the concept of dose. This can apply to both meprobamate, amobarbital, and other barbiturates.

Page 225, column 1, last two lines, to end of paragraph. I would criticize the "well-planned" experiments of Rickels and associates and Dickel and co-workers in that an inadequate sample size, range of dosage, and variety of barbiturates were used.

Page 225, last 16 lines. There is nothing about the study of Uhlenhuth and associates that offends common sense. It simply indicates that the doctor-patient relationship can be more important than the pill given. One cannot throw out data because it offends one person's common sense.

Small "therapeutic" doses of these agents were apparently insufficient to demonstrate a real pharmacologic effect in certain doctor-patient situations.

Page 226, paragraph 1. The statements are not based upon adequate evidence. Table III is inadequate in that it does not provide the concept of dose used. Furthermore, it is in disagreement with the data of other investigators whom the author fails to quote but is aware of from his reference list.

Page 226, paragraph 1, line 17. This sentence simply is not true! Deep anesthesia cannot be produced by small doses of chlorpromazine in animals.

Page 226, column 1, line 6 from bottom. The author fails to refer to all references in the literature when he makes a conclusion. Motor impairment has been described by many others. The author is so preoccupied with the 400 mg. dose of meprobamate that he fails to recognize that many of the effects which are lacking with the use of meprobamate are quantitative and not qualitative.

Page 226, column 2, paragraph 1. The term "nonspecific" depression is meaningless. At our present state of knowledge no one can decide what is "specific" and "nonspecific" depression of the central nervous system.

Page 227, concluding paragraph. This summary paragraph suggests bias by the author. For example, barbiturates are primarily useful as sedative-hypnotics. True! But so is meprobamate! The author fails to draw such a conclusion in spite of ample evidence. There is no universal agreement that meprobamate specifically relieves anxiety. How then can the author make such a conclusion?

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