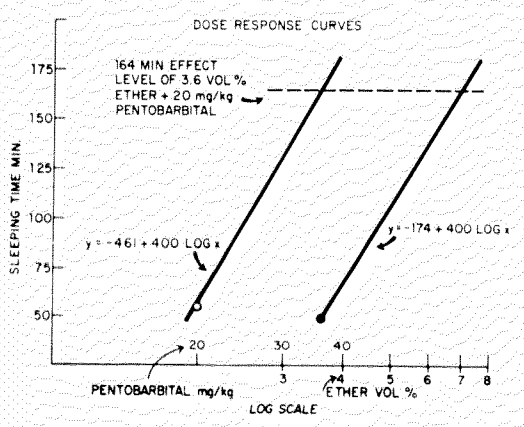
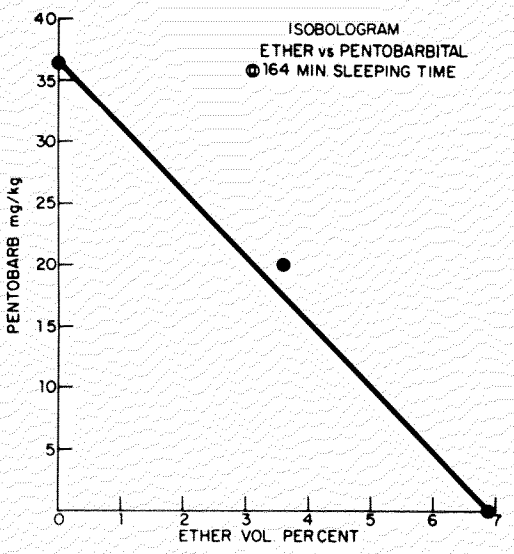
Potentiation

To the Editor.—Studies which apparently prove potentiation sometimes show something quite different when the data is analyzed completely. Therefore, I would like to mention some fundamental considerations related to the article by Baekeland and Greene (ANESTHESIOLOGY 19: 724, 1958), in the hope of avoiding further confusion. In their introduction they state that Greene and Whittaker (ANESTHESIOLOGY 18: 165, 1957) found an effect of pentobarbital plus diethyl ether which resembled potentiation.

When two active compounds are studied, as was done by Greene and Whittaker, they must be studied at more than one dose effect level if synergism is to be investigated. In the abstract (ANESTHESIOLOGY 18: 165, 1957) they do not state synergism has occurred but merely state the results they observed with pentobarbital, ether and the combination of pentobarbital and ether. That the sleeping time produced by the combination, 164 ± 72.8 minutes, was more than the arithmetic sum of the pentobarbital, 56.8 ± 20.6 minutes, plus the ether, 50 ± 8 minutes, sleeping time, could represent synergism, simple additivism or indeed antagonism. That it actually represents antagonism can best be understood from the following analysis: using the authors' values of 56.8 min. sleeping time following 20 mg./kg. of pentobarbital and 50.0 min. sleeping time following 3.6 volumes per cent diethyl ether and 164 minutes sleeping time following the combination assume a slope, b, for the dose effect equation $y = a + b \log x$, where y is the sleeping time in minutes and x the dose of the drugs, of $b = 400$. Then at 164 minutes sleeping time the equivalent dose of pentobarbital required to produce the same effect, 164 min. sleeping time, would be 36.5 mg./kg. and the dose for diethyl ether 6.95 volumes per cent. Plotting an isobologram (Loewe: Ärztl. Forsch. 285: 1, 1953) for these three points indicates that antagonism exists since the pentobarbital plus ether point falls NE of the equal effect line. Thus, whether antagonism, additivism or synergism occurs is a function of the slope of the two dose response curves. If the slope is 372 additivism is present, if it is greater than 372 antagonism is present, and if it is less than 372, synergism. Thus, in this case it is clear that the slope of the dose response curve must be known to make any conclusion relative to the presence of synergism or antagonism.





In the foregoing discussion I have assumed the dose effect slopes for ether and pentobarbital to be parallel. In all probability this is not true. If the slopes are not parallel the problem is more complicated. In any event it is necessary to have more than one point on the dose response curve before thinking about interactions and basic mechanisms of drug interaction. Therefore, before interpreting metabolic studies in terms of drug effects I think it best to determine what drug effects one is dealing with.

J. WELDON BELLVILLE, M.D.
Memorial Center
New York