vantage over morphine sulfate and is more expensive. . . . Demerol has a fairly good range of safety and it rarely depresses respiration. Untoward effects are dizziness, nausea and vomiting, weakness and syncope. Tremor and convulsions may occur when doses are excessive and repeated often. Demerol is a good substitute for morphine; therefore, it should have wider use in the aged.” 3 references.

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“According to the theory of narcosis proposed by Quastel and associates narcotics exert their effect by inhibiting certain metabolic processes in brain required for the metabolism of carbohydrate, upon which brain is largely dependent. . . . The site of action of narcotics has not been determined. . . . Accepting Quastel’s results there are two possible positions where narcotics may exert their inhibition—(I) by blocking the transfer of H from cozymase to flavoprotein and (II) by blocking the transfer of electrons from flavoprotein to cytochrome b. If the inhibition occurs at I in the above scheme one would expect to find an accumulation of reduced cozymase (coenzyme I) in the presence of narcotic. One would also expect to find that the transfer of hydrogen from reduced cozymase by flavoprotein in some suitable hydrogen acceptor was blocked by the addition of narcotics.

“If the above scheme represents a complete picture of the metabolic pathway in brain and if the block does not occur at I, by the process of elimination it must occur at II. There still remains the possibility, however, of another step in place of, or in addition to cytochrome b, between flavoprotein and the rest of cytochrome system. Further information on the position of the block may be obtained by determining the effect of narcotics on an enzyme requiring the cytochrome system but not cozymase. Such a system is that found in yeast, which oxidized lactic acid. In contrast to the animal laetic enzyme which requires cozymase, the yeast laetic enzyme does not require a coenzyme but transfers hydrogen by means of the dehydrogenase and the cytochrome system. If such a system is inhibited by narcotics it would be inferential evidence that the narcotic block was not at I, and that it could occur at II. The line attack outlined . . . was pursued.

“It has been found that reduced cozymase did not accumulate during the carbohydrate metabolism of brain in the presence of nembutal; and that the reaction

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\text{reduced cozymase + methylene blue flavoprotein} \rightarrow \text{cozymase + leuco methylene blue}
\]

was not affected by nembutal.

“These results indicate that the block was not at the position suggested as the first possibility. The oxidation of lactate by yeast was also found to be inhibited by nembutal. The fact that the yeast laetic enzyme, which unlike the enzyme in animal tissues does not require cozymase for activity, was inhibited, is further evidence that cozymase is not involved, and that the block occurs at cytochrome b or at some as yet unidentified step having properties similar to cytochrome b. We suggest that the narcotic may act by binding the reduced flavoprotein with cytochrome b (or other intermediate) and that the affinity of narcotic for this complex is greater than for the succinic dehydrogenase-cytochrome b complex which is not affected by low concentrations of narcotics.” 23 references.

J. C. M. C.