From their kinetic data on the oxidation of methanol by monkey ADH, Kini and Cooper estimated that 166 mg of the enzyme is necessary for the oxidation of 10·45 μmoles of methanol per min. The oxidation of 83 μmoles of methanol per min would then require about 1320 mg of ADH. These investigators find the average 3-kg monkey to possess 48 mg of liver ADH, a concentration which is in reasonable agreement with that estimated by Theorell and Bonnichsen[5] to occur in human liver. Thus, the measured monkey liver ADH can account for only 3·6 per cent of the observed methanol metabolism. If we assume that the 70-g liver reported by Kini and Cooper for the 3-kg monkey has a protein concentration of 18 per cent on the wet weight basis, the ADH necessary to metabolize the 83 μmoles of methanol per min (1320 mg) would constitute about 10 per cent of the total liver protein.

The estimation of the amount of enzyme required was made by Kini and Cooper with kinetic data obtained at 23° rather than 37°. Also, renal and pulmonary excretion of methanol were ignored, factors which would play a considerable role at the high blood methanol concentrations encountered in their studies. However, even if these considerations are taken into account, many times more enzyme would be needed to accomplish the observed rate of physiological oxidation than has been shown to be present in monkey liver. Thus it must be concluded that alcohol dehydrogenase does not play a major role in the physiological oxidation of methanol.

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Dear Sir:

The calculations that Drs. Mannering, Parks and Tephley make are based on the assumption that the 18 g of methanol administered to the monkey must be accounted for only in terms of oxidation. Gilger *et el.*[1] determined methanol levels in the plasma of ten monkeys which had received methanol at the same concentration we used in our studies (6 g/kg). When the mean methanol concentration is the plasma is extrapolated to zero time it can be calculated that 44 per cent of the alcohol was lost by pulmonary and renal routes. In our experiments the elimination of unchanged methanol by these routes amounted to 68 per cent.

In our rate figure for the disappearance of methanol from the body we used the total blood volume as a measure of this loss and, as the Wisconsin group points out, a more accurate measure necessitates the inclusion of the total body water. When our data are recalculated with this figure, and corrected for pulmonary and renal losses of methanol, we arrive at a value of 23 μmoles of methanol metabolized in the body per min. The same calculations applied to the data of Gilger *et al.* yield a figure of 28 μmoles. A reasonable agreement is apparent in these two studies, with the rate of methanol oxidation in the body averaging approximately 26 μmoles per min.* It is therefore necessary to determine whether sufficient alcohol dehydrogenase (ADH) is present in the body to account for this rate.

From Table 1 of our paper it can be calculated that monkey liver contains 48 mg of ADH and that to oxidize methanol at a rate of 26 μmoles per minute would require roughly 412 mg of the enzyme. This eight- to nine-fold discrepancy may be explained to a large extent by the following considerations: (1) The estimate of the total ADH activity in the supernatant extract of the liver mince is a minimal approximation because of the presence of DPNH oxidase in the preparation. (2) As stated in our paper, the enzyme determinations were performed at 23°, so that with the usual temperature effect on enzyme velocity prevailing it is not improbable to assume a threefold increase in ADH activity to

obtain at body temperature. (3) Finally, of course, one must take into account extrahepatic sources of of ADH such as kidney, spleen, etc.

It is obvious that the calculations made by us and by the Wisconsin group are really crude approximations and that neither group can make an unequivocal statement about the situation *in vivo* with respect to methanol oxidation. On the basis of studies with an inhibitor of catalase, the Wisconsin group feels that the catalase-peroxide system is involved in methanol oxidation. Arguments that this system does not operate *in vivo* are stated in our paper and also in a publication by Bartlett.[2] On the other hand, we have demonstrated that ADH can catalyse the oxidation of methanol, but the quantitative aspects of this activity are still open to question. The ultimate answer to the problem may be that both systems play a part.

* The *r* value of Widmark, which is quoted by the Wisconsin group, is not strictly applicable here, since it was obtained on human subjects.

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