## Distribution and Metabolism of Thiohexital

*To the Editor:*—The report by Dr. Mark and his colleagues (ANESTHESIOLOGY 29: 1159, 1968) contains several statements which, coming as they do from such eminent authorities, perplex me.

Your contributors strongly suggest that a greater degree of binding of drug to protein is correlated—other things being equal—with an increased rapidity of metabolism of drug by the liver. I would have thought the contrary to be so. Considering the situation in the serum alone, an increased degree of binding to protein implies that a smaller mass of drug is unbound in the blood traversing the liver, and hence available for transfer from the circulation into the hepatic cell. Assuming that the liver can "clear" the blood of all free drug, manifestly the greater the proportion unbound, the more rapidly will metabolism progress (provided that the hepatic cell can cope with the load). If, on the other hand, the speed at which free drug leaves the serum to enter the hepatic tissue is such that yet more drug is made available by the "unbinding" process to permit a further off-loading within the hepatic circulation, then consideration is to be given not primarily to the ratio of bound to free, but to the kinetics of the binding equilibrium.

Considering now the tissue–plasma concentration ratios: it is, I assume, accepted that under steady-state conditions, an equilibrium is achieved between the concentration of free (non-ionized) drug in plasma and that in extravascular tissue fluid. Thus, a highly-bound drug, such as thiohexital, will be found in low concentration as free drug outside as well as within the blood. However, presumably a drug which is highly bound to plasma protein is also highly bound to tissue protein. The postulate could be presented that if the various equilibria were to be satisfied (bound-to-free in plasma; free-to-free across the capillary membrane; bound-to-free in tissue fluid), increased binding would be associated with a greater proportion of drugs being relatively "fixed" in the tissues, resulting in a slower release for metabolism and excretion. Again, the kinetics of the binding and releasing processes could be the more important factor.

A second point: would Dr. Mark and his colleagues clarify their use of the term "biotransformation"? I find it difficult to understand how the half-life of the drug in plasma can be equated directly with the rate of biotransformation, if (as I have up to now understood it) the latter term implies an aspect of the degradation process.

Finally, Mark *et al.* state that they calculated the rate of metabolism "after allowing sufficient time (one and a half to two hours) for establishment of diffusion equilibrium of drug distribution between plasma and tissue fluids." This raises two questions: on what basis was the quoted interval chosen? and can a diffusion equilibrium be considered a meaningful concept when an agent metabolized so rapidly, administered as a single dose, is under consideration?

I raise these matters in a spirit of enquiry, as I consider that the whole fascinating problem of the influence of protein binding and tissue distribution upon drug metabolism is far from final elucidation.

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*To the Editor:*—Thank you for the opportunity to respond to the questions raised by Dr. Crawford concerning our studies with thiohexital. If he, who has obviously given much thought to these matters, is still perplexed, then others too will appreciate clarification.

First of all, the terms "biotransformation" and "metabolism" of the drug are preferred to "degradation," since chemical degradation implies disruption or alteration into smaller structures, whereas formation of complexes or syn-