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Albumin Binding and Hepatic Uptake: The Importance of Model Selection

Keyphrases □ Albumin—effect on removal of taurocholate by the liver □ Taurocholate—removal by liver, albumin

To the Editor:

Dr. Colburn's letter to the *Journal* in March 1982 (1) purports to invalidate a conclusion we published earlier in the *Journal of Clinical Investigation* (2) concerning the role of albumin binding on the removal of taurocholate by the perfused rat liver. Having just learned of Colburn's communication we offer the following rebuttal. Better late than never!

The observations we reported (which are not in contention) show that the extraction fraction of taurocholate declines only slightly when the perfusate albumin concentration is increased, even though this maneuver reduces the free (unbound) fraction of taurocholate by a factor of five. The table shows the data for rat livers perfused at the same flow rate and with the same total concentration of taurocholate (18 μM).

Albumin Concentration (g/dl)	Free Fraction of Taurocholate in Perfusate	Taurocholate Extraction Fraction
0.5	0.57	0.97
5.0	0.11	0.86

The objective of the experiment was to learn what these numbers imply about the apparent rate constant for hepatic uptake, given that the low concentration of taurocholate ensures that both the binding reaction in extracellular fluid and the removal process are operating far removed from saturation and that the binding reaction is fast enough compared with the removal rate to be considered at equilibrium. These stipulations are also not in contention. Instead the controversy focuses on the choice of an appropriate model with which to interpret the data.

Colburn prefers to model the extracellular fluid as a single homogeneous compartment in which each liver cell is exposed to the same taurocholate concentration—the so-called "lumped" or "venous equilibrium model." In this case the steady-state conservation equation is:

$$Fu_0 = \psi VKu_v + Fu_v \qquad \text{(Eq. 1)}$$

in which ψ is the free fraction, F is perfusate flow, K is the rate constant for removal of free taurocholate, and V is the extracellular volume. The terms, u_0 and u_v, in Eq. 1 are the inflow and outflow concentrations of total taurocholate, respectively. Rearranging Eq. 1 yields:

$$K = FE/[\psi V(1 - E)] \qquad \text{(Eq. 2)}$$

in which the extraction fraction, E, is $(u_0 - u_v)/u_0$. Equation 2 is the one suggested by Wilkinson and Shand (3) to whom Colburn appeals for support.

We have preferred to use a so-called "distributed" model accounting for the decline in taurocholate concentration that occurs along each sinusoid. The conservation relation for a single sinusoid is in this case:

$$F\frac{du}{dx} = -\psi\gamma Ku \qquad \text{(Eq. 3)}$$

where x is the sinusoidal volume running from $x = 0$ at the portal inlet to $x = V$ at the hepatic venous outlet and γ is the ratio of the sinusoidal volume to the volume of the Disse space divided by the sinusoidal volume. The solution to Eq. 3 is:

$$K = -F\ln(1 - E)/\psi\gamma V \qquad \text{(Eq. 4)}$$

If one now computes the ratio of the K values from the observations made with high and low concentrations of albumin, the results are strikingly different depending on the choice of the model.

$\frac{K \text{ at high albumin}}{K \text{ at low albumin}}$	Lumped Model	Distributed Model
	0.98	2.9

The interest in these calculations derives from the fact that both models are constructed on the conventional teaching that only free taurocholate is available for removal. If we accept Colburn's model this assumption appears confirmed because the calculations yield the expected identity of the rate constants. If we accept the distributed model, however, the data contradict the conventional teaching because in this case the rate constants differ by nearly a factor of three. The direction of the discrepancy is such that liver cells appear to enjoy some special mechanism for enhancing the dissociation of the albumin–ligand complex—in effect making more free taurocholate available to liver cells than the conventional teaching would predict. There is, in fact, a growing body of additional evidence to support this conclusion (4–7), but our concern here is with the question of which model to accept.

Those who choose the Colburn model will have to decide where the change from u_0 to u_v occurs. Plainly it cannot be attributed to the removal of taurocholate by hepatocytes because the model requires that all liver cells be exposed to the same concentration. Alternative choices that the drop in concentration occurs in the presinusoidal portal circulation or in the postsinusoidal hepatic veins would not only be anatomic nonsense but would imply that the calculated rate constant has nothing whatever to do with the transport function of liver cells. On this basis we conclude that although Colburn's analysis of the data appears to confirm a widely held preconception, it is physiologically irrelevant. His model simply does not describe a real liver.

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The distributed model, though possibly oversimplified as well, is certainly a much better representation of the physiological facts. It may even be correct, because on closer inspection (2, 4) the distributed model turns out to be free of restrictive assumptions that the sinusoids are of uniform bore or that each liver cell has the same transport capacity. The interpretation moreover is virtually independent of variations in the distribution of flow to a large population of sinusoids.

Compartmental analysis is a powerful tool for gaining new physiological insights. Its utility, however, depends critically on the validity of the underlying assumptions. If these are wrong so will be the results. The worst of this is that model-dependent interpretations of the data can rarely, if ever, be used to validate the preconceptions on which the model was constructed. We suggest that Colburn may wish to reconsider the simplistic assumptions on which his model rests before taking too seriously the conclusions that flow from it.

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Albumin Binding and Hepatic Uptake: The Importance of Model Selection—A Response

Keyphrases □ Albumin—effect on removal of taurocholate by the liver □ Taurocholate—removal by liver, albumin

To the Editor:

Forker and Luxon have written an interesting rebuttal to my earlier communication (1). However, it only serves to confuse the issue even more.

Forker and Luxon presented data in their original report, which they interpreted using the parallel tube or "distributed" model (2). They concluded that albumin helps mediate the removal of taurocholate from a perfused liver preparation. Using the same data, I presented an alternate interpretation using the widely used and accepted well-stirred, venous equilibrium or "lumped" model. I concluded that albumin does not mediate taurocholate removal.

In their rebuttal (3) Forker and Luxon attempt to lend physiological credence to the parallel tube model at the expense of the well-stirred model. Neither model is physiologically realistic in that the liver is neither a well-stirred beaker nor is it a series of parallel tubes.

The theoretical basis for each of these two models has been developed and discussed in depth (4–6). Although the well-stirred model has been shown to be more predictive than the parallel tube model, in some cases (7–8) it would seem that neither model holds a universally distinct advantage over the other and that attributing physiological meaning to parallel tube model-based conclusions, which contradict previous work in the area, would seem unjustified without further substantiation. Unless the data are unequivocal, parsimony should rule, and if a model must be chosen the one that is time proven (7–9) should prevail.

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