study, we rely on the principle of truth in scientific communication. Acute HCV research is moving east where there is a real clinical problem with the disease and the ability to perform larger, equally well-run clinical trials with all HCV genotypes included.

Finally, an erratum with correction missed in the proofs had already been submitted to HEPATOLOGY prior to receipt of the letter from Wedemeyer and we are sorry for the confusion on the part of the readers.

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The Brain Permeability-Surface Product for Ammonia

To the Editor:

In 1991, we reported an increase in the permeability surface area product (PS) of the blood-brain barrier (BBB) to ammonia in patients with severe liver disease and minimal hepatic encephalopathy (mHE).[1] We thought this explained the development of "toxin hypersensitivity" as disease progresses, a phenomenon we documented in animals[2] and why patients with mHE might have normal blood ammonia levels.

This finding is challenged by Keiding et al., who report a reduction in the PS product for ammonia in patients with cirrhosis with and without HE[3]. They attribute the difference to superior imaging and physiological modeling. Data from these two studies are shown in Table 1.

To evaluate these data, it is necessary to consider the validity to the assumptions of the models and whether the results agree with other published data. Our model was extremely straightforward and made few assumptions aside from irreversible trapping of ammonia by the brain. Keiding et al. used a graphical approach that requires serial PET images and arterial blood samples[4]. This model assumes bidirectional movement of ammonia across the BBB with irreversible trapping. Keiding et al. complicate the model by including ^{13}N-urea and ^{13}N-glutamine in the intravascular compartment in addition to ^{13}N-ammonia. They assumed that urea crosses the BBB, without metabolic trapping, with kinetics that are identical to water, an assumption at odds with other data.[5] These deviations require an explanation beyond their comment that urea was added to improve the goodness of the fit to the model. Their assumption that the intravascular compartment occupies 1% of the brain volume is about one fourth the value reported by others[6]. It is also puzzling that mean PS values computed using their equation 1 and mean values of CBF and K_1 in their Table 2, bear little resemblance to PS values they report, as shown in the table.

The CBF measurements made by Keiding et al. don't show the expected reductions in patients with overt HE.[7] The small standard errors they report imply little difference between patients with grade IV HE and those less severely impaired. The failure to observe a reduction in CBF requires explanation, particularly since this variable appears twice in the formula for computing PS (their equation 1).

Finally, they report that the rate constant for conversion of ammonia to glutamine is 0.1 per minute. This is in contrast to the data of Cooper et al., who reported that the $t_{½}$ for the trapping reaction was 1-3 seconds, or less.[8] What effect would the insertion of this value into model equations have on the PS product?

Table 1. Comparison of Study Data

Source	PS Control	PS Minimal or no Overt HE	PS Overt HE	CBF Control	CBF Minimal or No Overt HE	CBF Overt HE
Lockwood et al.[1] mid-thalamic slice values ± SD	0.13 ± 0.03 mL/g tissue/min	0.22 ± 0.07* mL/g tissue/min	–	0.58 ± 0.12 mL/g tissue/min	0.46 ± 0.16 mL/g tissue/min	–
Keiding et al.[3] cortex values ± SEM	0.34 ± 0.03 mL/mL tissue/min	0.31 ± 0.03* mL/mL tissue/min	0.21 ± 0.02* mL/mL tissue/min	0.47 ± 0.03 mL/mL tissue/min	0.44 ± 0.03 mL/mL tissue/min	0.41 ± 0.04 mL/mL tissue/min
Calculated from Keiding et al., Table 2 CBF and K_1	0.45 (cortex) mL/mL tissue/min	0.57 (cortex) mL/mL tissue/min	0.50 (cortex) mL/mL tissue/min	–	–	–

*Denotes statistically significant difference from control value at $P \leq .05$.
Values for cortex from Keiding et al.[3] were selected as this was the only site at which differences were found in both groups of patients.
PS product $= -\ln(1 \times K_1/CBF)CBF$.

Progress is based on the development of better methods to address important problems. When disparities in results arise, it is essential to employ multiple methods and careful tests of validity to avoid error. The PS product issue is important and a great deal of our understanding of the role of ammonia and the cerebral dysfunction associated with HE depends on resolving this dilemma.

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Reply:

We are pleased by the interest of Drs. Lockwood and Wack in our recent ^{13}N-ammonia PET study on brain ammonia metabolism in patients with cirrhosis and clinically manifest hepatic encephalopathy (HE).[1] Since our results apparently differ from results by Lockwood and coworkers,[2-4] Drs. Lockwood and Wack expressed concern about our modeling. This gives us the opportunity to clarify the concepts of PET estimation of the permeability-surface area products (PS) for the blood-brain-barrier (PS_{BBB}) and the metabolism (PS_{met}) (Fig. 1).[1,5]

Unfortunately in our article[1] there was an arithmetical error in the calculations of PS_{BBB}. A corrected Table 2 is given in a "Corrections" in this issue of the Journal. Mean PS_{BBB} values in the group of patients with cirrhosis and HE were lower than mean values in the group of healthy controls but the difference was not statistically significant. This is in agreement with another recent dynamic ^{13}N-ammonia PET study.[6] Thus, the results still indicate that the elevated blood ammonia and not changed brain ammonia kinetics is the more important factor for the increased ammonia uptake in patients with HE.

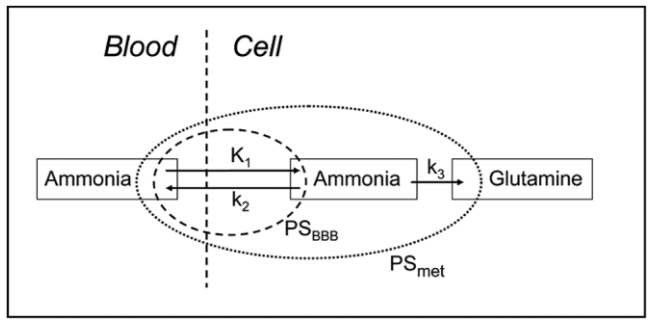

Fig. 1. K_1, unidirectional clearance (mL blood/min/mL tissue); k_2, back-flux rate constant (per minute), k_3, rate constant of enzymatic trapping (per minute). PS_{BBB} (mL blood/min/mL tissue) is given as $-CBF\ \ln(1\text{-}K_1/CBF)$. PS_{BBB} is a measure of the capacity of substrate transfer across BBB. Ammonia diffuses freely across the BBB.[9,10] $PS_{metabolism}$ is a measure of the combined transfer of ammonia from blood to cells and the metabolic trapping within the cells. $PS_{metabolism}$ is given as $-\ CBF\ \ln(1\text{-}K_{metabolism}/CBF)$ where $K_{metabolism} = K_1\ k_3/(k_2 + k_3)$.

Calculation of PS_{BBB} requires dynamic PET recording starting at the time of injection since it includes K_1 (Fig. 1). The estimation of K_1 is calculated from the initial time-course of tissue radioactivity and is very sensitive to changes hereof. Lockwood's group calculated PS-values from static PET recordings,[2-4] which yield no specific information on the initial time-course of tissue radioactivity. Their PS-values are therefore an opaque mixture of PS_{BBB} and $PS_{metabolism}$ and not comparable with our PS_{BBB} -values.

Duplicate cerebral blood flow (*CBF*) measurements in our study deviated less than 5% in each subject.[1] The *CBF* in the healthy controls and in the patients with cirrhosis without clinical signs of HE were similar to the *CBF* in comparable individuals in other studies.[4,6,7] We therefore see no reason for doubting the validity of our *CBF* measurements in chronic liver patients with overt HE.

Our philosophy on kinetic modeling is to make the models as physiologically correct as possible while keeping the number of parameters as low as possible. The simple model proposed by Lockwood and coworkers assuming irreversible trapping of ammonia may be justified in view of their study design and data, among which they assumed blood ^{13}N-ammonia to be cleared within 10 minutes. In our study, however, blood ^{13}N-ammonia fraction decreased throughout 30 minutes but never reached zero in any subject, and we furthermore measured specific ^{13}N-metabolites, which all justifies a more complex model.[1,8]

The volume of 0.01 used for the ammonia metabolites does not equal the vascular volume of the brain, but is a kinetic distribution volume which is commonly used in PET kinetics.

Contemporary PET technology with high spatial and temporal resolution in conjunction with proper mathematical-physiological models fitted to the data represents to us an excellent method to address the question of ammonia metabolism in patients with overt HE.

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