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# Letters to the Editor

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The presence (in blood or urine), in high quantities, of the homoanalogues of substrates of the urea cycle in the presence of argininosuccinate synthetase deficiency gives rise to two different interpretations. Scott-Emuakpor *et al.* (10) postulate the existence of a late developing urea cycle for homoanalogues. Levin *et al.* (4) reject this possibility and tend rather towards the hypothesis of a competitive inhibition of lysine metabolism by citrulline.

Our point of view is different from the two preceding ones. We believe that lysine and homocitrulline accumulate because they are, respectively, substrates of ordinary ornithine carbamyltransferase (O.C.T.) and of ordinary argininosuccinate synthetase (A.S.S.).

With regard to O.C.T., we base our argument on two lines of reasoning. (*1*) Whenever we have observed OCT deficiencies, we have encountered hyperlysinemia as a constant factor. Before our patients were placed on a diet, the lysine level was always 2 or 3 times normal: 52 μmoles for the first patient (8), 72 for the second, 41.3 for third (9), 71 for the fourth (1); normal limits are between 11.4 and 26.9 μmol/100 ml serum. In addition, one of our patients underwent a lysine load and the peak of lysine was much higher than that of the control subject (1). On the other hand, two other studies (3, 4) have shown, utilizing purified bovine hepatic OCT, that lysine is a substrate of OCT with an affinity about 50 times less that for ornithine. Thus, in OCT deficiency the hyperlysinemia would be a consequence of a block on a normal metabolic pathway, however minimal.

One cannot be certain with regard to homocitrulline as a substrate of A.S.S., for this enzyme has not yet been completely purified (7). However, recently, Ratner (6) has obtained 10% of the activity with homocitrulline as substrate of bovine A.S.S.

Nevertheless, the accumulation of lysine and homocitrulline in A.S.S. deficiency is an indirect argument in favor of this hypothesis.

The accumulation of homocitrulline in persistent hyperlysinemias (2) would arise from the same mechanism: lysine not being catabolized by the main pathway which is blocked would shift to the urea cycle, in which the first step is the formation of homocitrulline from lysine by the action of O.C.T.

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11. Requests for reprints should be addressed to: C. Polonovski, M.D., Hôpital Trousseau, 26 Avenue du Dr. Arnold-Netter, 75571 Paris Cedex 12, France.
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We have read with great interest the letter written by Dr. Cathelineau *et al.* They agree with us that the high levels of lysine, homocitrulline, and homoarginine found in argininosuccinate synthetase deficiency do not necessarily indicate the existence of an alternative urea cycle, but they further conclude that the increases follow directly from the defective urea cycle enzyme and are not due to inhibition of lysine catabolism by citrulline. In support of their conclusion they report finding high levels of lysine in untreated patients with ornithine transcarbamylase deficiency. Although we have always found lysine levels to be normal in patients with this disease investigated after treatment has started, we have also observed an elevated level of lysine in plasma on a single occasion in an untreated patient (2). However, we have interpreted this finding differently. Ammonia has been reported to inhibit the catabolism of lysine via saccharopine (1) and we believe that inhibition by ammonia is the most likely explanation of the high lysine levels in untreated ornithine transcarbamylase deficiency. After treatment by low protein intake, levels of ammonia in blood are markedly reduced so there would be less inhibition of lysine catabolism as well as a reduced intake of lysine, and this would explain the normal lysine levels found in treated patients. There may be some inhibition of lysine catabolism by ammonia in argininosuccinate synthetase deficiency, in addition to the proposed inhibition by citrulline. The hypothesis that the raised levels of lysine in patients with urea cycle defects are caused by inhibition of a major lysine catabolic pathway seems more plausible than that they result directly from defects in a pathway which by all available evidence is of little or no importance for lysine metabolism. The significance of a metabolic pathway may best be judged by the build-up of metabolites when a defect occurs in that pathway; furthermore, the levels of homocitrulline in argininosuccinate