synthetase deficiency are extremely small compared with the levels of citrulline, even if it is assumed their elevation is a direct consequence of the enzyme defect. Also homoargininosuccinic acid has yet to be reported as present in argininosuccinate lyase deficiency.

Finally, we would like to point out a printer's error in our original letter, which may have confused some readers. Saccharopine is similar in structure to argininosuccinic acid, and not as stated.

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On a Late Developing Urea Cycle

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The interpretation given by Cathelineau, Saudubray, Charpentier, and Polonovski (1) to the presence of high quantities of the homoanalogues of substrates of the urea cycle in the presence of argininosuccinate synthetase deficiency is very interesting. It, in fact, confirms our published work (6) on lysine transcarbamylation. In that publication, we showed (*1*) that the conversion of lysine to homocitrulline is similar to the conversion of ornithine to citrulline, (*2*) that in the conversion of either substrate, the same enzyme is involved, because of evidence of some competition of both substrates for the same enzyme, and (*3*) that in the reaction involving either lysine or ornithine, carbamylphosphate is required, which implies that these are transcarbamylation reactions and also suggests that ornithinecarbamyltransferase (OCT) is the enzyme involved.

We have also implied that the affinity of the enzyme for lysine is much less than that for ornithine (an affinity of 50 times less will be a fair approximation). In this regard, therefore, we are in agreement with the authors.

This fact notwithstanding, our postulate (5) of the existence of a late developing urea cycle still stands. We did not base our postulate solely on our observation of elevated homoanalogues of substrates of the urea cycle. It was also based on (*1*) the patient's ability to regulate his blood ammonia levels (although slowly) even on a high protein diet; and (*2*) the patient's ability to synthesize normal amounts of urea. If one does not accept our postulate, then homocitnilline and citrulline which are respectively the products of lysine and ornithine transcarbamylations will be "dead-end" products in argininosuccinate synthetase (A.S.S.) deficiency.

We felt, in reaching our conclusion, that the transcarbamylation of both ornithine and lysine to "dead-end" products cannot alone account for the normal levels of ammonia reported in our patient. We also felt that the transamidation of lysine to homoarginine reported by Ryan *et al.* (4) and the subsequent hydrolysis of the homoarginine to urea cannot alone account for the normal urea levels reported in our patient.

Ratner's work (3) has now provided a fresh evidence for the existence of our postulated cycle. He has obtained 10% bovine A.S.S. activity with homocitrulline as substrate.

Our postulated cycle is shown in Fig. 1. In the figure, *A* is the OCT-catalyzed lysine transcarbamylation shown by Scott-Emuakpor and Kohrman (6), suggested by Ryan *et al* (4), and now reported by Cathelineau *et al.* (1); *B* is the condensation of homocitrulline and aspartate by the enzyme A.S.S. to homoargininosuccinate (A.S.A.) recently shown by Ratner (3); *C* is the splitting of A.S.A. to homoarginine and fumarate by the enzyme argininosuccinase. The reverse of this reaction had been established by Strandholm *et al.* (8), which implies that the reaction indeed exists. *D* is the hydrolysis of homoarginine to urea by the enzyme arginase. This reaction has been known for some time (4), but had been dismissed as being of no practical consequence. Scott-Emuakpor (7) has shown that in this hydrolysis, lysine, as well as urea, is produced.

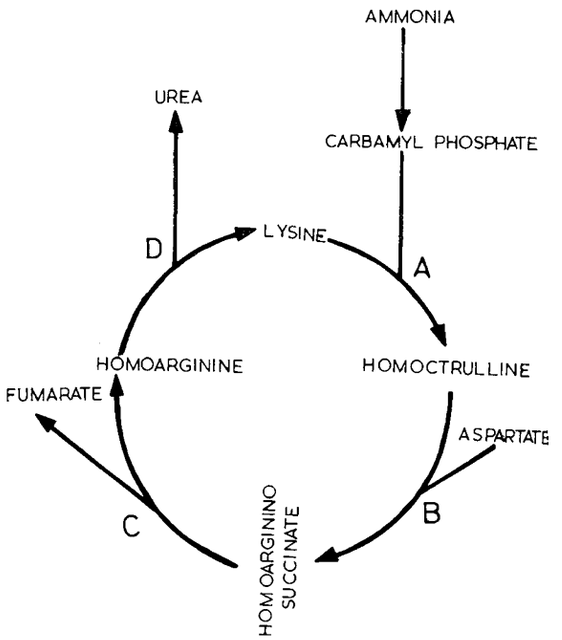

Fig. 1. Postulated lysine-urea cycle. For explanations of *A–D*, see the text.

It can be seen, therefore, that the recent work of Ratner (3) tied together the loose point of our postulated cycle. I do not think one can overlook the evidence before us.

It is for these same reasons that I find it difficult to accept the hypothesis of Levin *et al.* (2) that the elevated levels of homoanalogues of the urea cycle substrates can be accounted for by a competitive inhibition of lysine metabolism by citrulline.

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