letters to the editor

The following is the abstract of the article discussed in the subsequent letter.

Adey, Deborah, Rajiv Kumar, James T. McCarthy, and K. Sreekumaran Nair. Reduced synthesis of muscle proteins in chronic renal failure. Am. J. Physiol. Endocrinol. Metab. 278: E219–E225, 2000.—Muscle wasting and weakness occur frequently in patients with chronic renal failure. The mechanism(s) by which these abnormalities occur is unclear. We hypothesized that such findings were due to defective muscle protein synthesis. We measured synthetic rates of mixed muscle proteins, myosin heavy chain, and mitochondrial proteins in serial muscle biopsy samples during a continuous infusion of [1-13C]leucine from 12 patients with chronic renal failure and 10 healthy control subjects under identical study conditions. Patients with chronic renal failure have significantly lower synthetic rates of mixed muscle proteins and myosin heavy chain (27 and 37% reductions, respectively, \( P < 0.05 \) and \( P < 0.02 \)). Significant declines in the synthetic rates of muscle mitochondrial protein (27%) \( (P < 0.05) \), muscle cytochrome c-oxidase activity (42%) \( (P < 0.007) \), and citrate synthase (27%) \( (P < 0.007) \) were also observed in patients with chronic renal failure. The synthetic rates of muscle proteins and activity of mitochondrial enzymes were negatively correlated to the severity of renal failure. These results indicate that in chronic renal failure there is a decrease in the synthesis of muscle contractile and mitochondrial proteins and a decrease in muscle mitochondrial oxidative enzymes. Reduced synthetic rate of several muscle proteins is the likely biochemical basis of muscle loss and muscle weakness in people with chronic renal failure.

Why Is Muscle Protein Synthesis, But Not Whole Body Protein Synthesis, Reduced in CRF Patients?

To the Editor: Adey et al. (1) recently published an interesting study, unique in its comparison of systemic and local protein metabolism in chronic renal failure (CRF). Using muscle biopsies, they found a 27% reduced mixed muscle protein synthesis and a 37% reduction of myosin heavy-chain synthesis. The systemic findings obtained with whole body leucine kinetics show overall protein metabolism to be similar to that of normal controls. This appears at first sight to be a discrepancy and receives little attention in the discussion. We believe, however, that it may be a crucial finding. Possibly the decreased muscle protein synthesis is not a defect but an adaptive mechanism. Thus, by decreasing protein synthesis in muscle, amino acids are made available for synthesis of proteins serving other purposes, such as immunological ones. If uremic toxins would specifically cause a decrease in muscle protein synthesis, they would also be likely to cause decreased systemic protein synthesis. Because this is not the case, the effect may be similar to the one described by Mansoor et al. (2), who found a 50% reduction of muscle protein synthesis whereas whole body protein synthesis increased by 28%. In these experiments, there was an evident shift of protein synthesis from muscle protein to the immune system. This is probably also the case in a more chronic manner for CRF patients (3). The possible connections between low-grade inflammation of uremia on the one hand and the uremic complications on the other hand are beginning to attract more attention. It may well be that low-grade inflammation is a major cause not only of the accelerated atherosclerosis of uremia but also of the changes in protein metabolism described by Adey et al.

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REPLY

To the Editor: In their Letter to the Editor, Veeneman et al. proposed an interesting hypothesis about our observation (1) that, whereas fractional synthetic rates of muscle proteins (myosin heavy, mitochondrial protein, and mixed muscle proteins) are lower in people with chronic renal failure (CRF), no differences in whole body leucine kinetics between CRF and healthy control subjects were observed. In the absence of any direct measurements of synthesis rate of nonmuscle proteins, the above hypothesis remains to be tested. The comparison of whole body data between two groups of subjects with different body compositions must be interpreted with caution. Unlike fractional synthesis rates of muscle proteins, whole body leucine kinetics are normalized for fat-free mass (FFM). FFM
was measured by dual-energy X-ray absorptiometry (DEXA). DEXA measurement of FFM does not distin-
guish between muscle mass and water. It is likely that we may have overestimated FFM on CRF patients who may have water retention. A similar situation exists in older subjects with sarcopenia, in whom FFM measurement by DEXA overestimated lean mass because of increased body water (2). It is also unclear whether changes in the composition of nonmuscle tissues occur in people with CRF. It is, therefore, prudent not to make any conclusions on whole body leucine kinetic values on the basis of cross-sectional comparison between populations with different body compositions. The proposed hypothesis by Veeneman et al. could be tested by directly measuring synthetic rates of proteins involved in the immunological or inflammatory re-

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