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Letter to the Editor

Dear Editor

I am pleased that Roy Talmage continues to share my interest in plasma calcium homeostasis[1],* and also pleased with our agreement that the locus of control is the quiescent surface of bone[2]. For many years Talmage proposed that bone lining cells maintained an outwardly directed calcium pump influenced in some way by parathyroid hormone (PTH)[3], to balance the inward flux due to the poor solubility of hydroxyapatite[4]. No evidence for such a pump has ever been found, and the proposal was criticized by Felix Bronner as energetically implausible[5]. As an alternative, Bronner proposed that calcium binding sites of varying affinity (expressed as K_m) were located on the bone surface[5]. Such binding sites could account for many experimental observations[2], but they were and have remained chemically undefined, and the proposal did not readily account for the effect of PTH.

I doubt that Talmage's new proposal will work. In Figure 1, which leaves out the lining cells, the concentration of free calcium (I prefer this term to ionized calcium, since all calcium in the body is ionized) in the fluid between the bone surface and the mesh of calcium binding non-collagenous proteins (NCP) would be dictated by the physical chemistry of the surface mineral. The NCP would equilibrate with this concentration, just as calcium binding proteins in plasma (mainly albumin) equilibrate with the prevailing free calcium concentration in plasma[6]. Protein binding may act as a buffer to reduce the rate of change, but cannot affect the equilibrium concentration. Proteins cannot move calcium unless the protein-calcium complex itself moves, as during intestinal calcium absorption[7]. Talmage further suggests that PTH raises the level of equilibration between blood and bone by increasing the size of the exchangeable fraction, but large increases in the exchangeable calcium pool in Paget's disease and hyperthyroidism may have no effect on plasma concentration.

To me, a much more likely role for NCP is the one suggested many years ago by Bill Neuman[8]. The only form of bone mineral sufficiently soluble to maintain a normal plasma calcium concentration is brushite (secondary calcium phosphate, $CaHPO_4.2H_2O$). NCP stabilizes brushite at physiologic pH and temperature, preventing its transformation to apatite even in the presence of apatite[8]. Both osteocalcin and osteonectin are able to inhibit growth of hydroxyapatite crystals[9]. Whatever the mechanism of the biological equilibrium between blood and bone, the level of equilibration must be controlled by PTH[10]. As suggested many years ago by Chris Nordin and Jim MacGregor[11], this could be accomplished by small changes in the local pH, which will alter the activity product for brushite, independent of the NCP effect[8].

These were almost Neuman's last papers, published posthumously. One of the first things I learned from him was the need to think in thermodynamic terms, and to appreciate the distinction between *concentration* and chemical *activity*. He stated[4]: "Activity coefficients are of the utmost importance. ... Since these activity corrections are of considerable magnitude, they *cannot be ignored*." Regrettably, the terms activity coefficient and activity product have largely disappeared from the biomedical literature. The premier award of the ASBMR is named for Neuman, but what he tried to teach us is in danger of being forgotten.

References

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** Note: A response by Professor Roy V. Talmage will not be forthcoming. He chooses not to argue in public, but will continue with their discussion in private.*