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Jerry Yee
Henry Ford Health, JYEE1@hfhs.org

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EDITORIAL

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The elaboration of the interactions among calcium, phosphate, and parathyroid hormone (PTH) has somewhat followed the evolution of astronomy. Ptolemy proposed that the sun revolved about the earth, and his geocentric view of our solar system was accepted for centuries. The proof of a heliocentric system of circumscribed elliptical not circular orbits required the efforts of Copernicus, Galileo, and Kepler. Today, with superior instrumentation, contemporary cosmologists generate and test hypothesis at comparative light speed. Similarly, the roles played by calcium and phosphate, under the gravitational influence of PTH, have assumed primacy at various points during the elucidation of the pathogenesis of chronic kidney disease-mineral and bone disorder (CKD-MBD). In this phosphocentric issue of *Advances in Chronic Kidney Disease*, our Guest Editors, Eleanor Lederer and Moshe Levi, have coordinately integrated inorganic phosphate into the expansive pathophysiology of CKD-MBD.

The authors recruited for this task multiple scientific observations gleaned with the aid of molecular tools to make their points. With these enhancements has come a renewed interest in the field, and the rarest of celestial events has occurred—the syzygy—an alignment of the spheres of calcium, phosphate, and PTH. The Guest Editors had from the outset mapped out a course of alignment for the authors who would reconcile much of what we have postulated and learned in the past half decade regarding the pathogenesis of CKD-MBD, with inorganic phosphate as the central theme. The authors delineate a new presentation of the galaxy of CKD-MBD and introduce new players within this particular cosmos of CKD.

The basic tenets still hold. As glomerular filtration declines, phosphate retention occurs and is toxic, exerting diverse effects on vascular smooth muscle cells, among others. Calcium, which had originally been at approximately the same plasma molarity as ionized calcium, is now silently complexed by a rising serum phosphate. This occurs in concert with a corresponding decline in fetuin levels. Fetuin, also termed α_2-Heremans-Schmid glycoprotein, maintains phosphate in a quasi-stable complex with calcium, thus inhibiting untoward calcification.[1] Even mild disruption of this equilibrium permits fusion of calcium and phosphate and underpins the beginning of the cardiovascular risk associated with advancing CKD, namely, de novo and accelerated calcification of the vasculature. This response is abetted by the process of hemodialysis, and adjustments in dialysate baths are required. These events likely require phosphate "sensing," and involve evolutionary conservation of these molecular sensors from their prokaryotic origins.[2] The intestinal lumen exhibits phosphate sensing, and phosphaturia is initiated in advance of absorptive hyperphosphatemia, sentiently pre-empting elevations of PTH. Activation of these sensors deploys multiple downstream events involving cellular metabolism and likely those related to differentiation and proliferation. However, all of this occurs despite the compensatory onset of secondary hyperparathyroidism onset of secondary hyperparathyroidism and elevation of phosphatonins.[3]

Like black holes, phosphatonin effects were theorized first and then discovered because the entity itself remained ethereal. To have characterized them as nebulous would have been generous. Later than sooner, they were found and the family of phosphatonins has been partially described (see Table 1 by Razzaque, p. 96). The most fully characterized phosphatonin is fibroblast growth factor 23 (FGF-23) and is elaborated by osteocytes and osteoblasts.[4] FGF-23 appears early during the course of CKD and its secretion is promoted by hyperphosphatemia and $1,25(OH)_2D_3$. FGF-23 also increases osteoblastic transcriptomal activity, thus rendering a calcium-laden phenotype that translates clinically as impaired vascular compliance and heightened pulse wave velocity, secondary to vascular structural alterations (eg,

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osteochondrogenic transformation, calcification, and elastic degradation) that give rise to windkessels.

FGF-23 downregulates proximal tubular 1-alpha-hydroxylation of 25(OH)D3 in contradistinction to PTH and, working in conjunction with klotho, amplifies PTH's effects on the apical, proximal tubular sodium-dependent phosphate cotransporter (see Cover of this issue).[5] This family of phosphate co-transporters includes Npt2a, Npt2c, and PiT2 and is regulated by physiological stimuli that include PTH, glucocorticoids, steroids, vitamin D, and endocrine hormones, among others.

In addition, FGF-23 is also positively regulated by dietary phosphate consumption and active vitamin 1,25 $(OH)_2D$, recapitulating and reaffirming the postulates of those who expounded on the primacy of phosphate and whose experimental instruments were on par with refractor telescopes of the ancient astronomers. Significantly, dietary privation of phosphate increases the lifespan of klotho- and FGF-23-knockout mice.[6] However, the klotho co-receptor, somewhat portrayed as the binary star of FGF-23, may escape the orbit of FGF-23 and act independently of it, for example, during regulation of the subfamily V transient receptor potential cation channel. Unsurprisingly, FGF-23 like its inducer, phosphate, is now associatively coupled to future adverse cardiovascular events and kidney disease progression.[7] Please recall that despite a worldwide dearth of phosphate, dietary phosphate is in surfeit, surreptitiously yet robustly entering our food chain as United States Department of Agriculture-unlabeled food preservatives.[7] Perhaps, in the future, regulation of gut sodium-dependent phosphate cotransporter, Npt2b, will be possible, thereby offsetting to some extent our inability to enforce dietary phosphate restriction.

However, as clearly pointed out by Kendrick and colleagues, we have excellent epidemiological data on elevated phosphate levels and excessive cardiovascular events that do not translate directly to precise consensus-based clinical practice guidelines.[8] Are we light-years away because hard endpoint analysis and randomized, controlled clinical trials that provide this information remain as distant as the stars? For the present, trend analysis of the parameters of CKD-MBD is recommended by KDIGO rather than therapy based on isolated calcium, phosphate, and intact PTH levels.

To conclude, as the multiple efforts of the astronomers reconciled the fundamental truths of our solar system, so too have our authors reconciled some of the mysteries of the pathobiology of CKD-MBD. With time, the model changed, and not gradually, at times propelled forward by ideas considered heretical (Galileo) or revolutionary in scope. The Guest Editors have assembled a group of papers that have aligned the interdependent forces of calcium, phosphate, and PTH axis. None of them is "fixed in the sky," and there is continual interchange among them. Calcium and PTH have since long been accorded their dues and finally, inorganic phosphate claims its place among the members of this syzygy. With time and greater accrual of knowledge regarding the phosphatonins, this alignment will become even more precise.

Finally, let us return to our earthly plane to hail our annual nephrologic event, World Kidney Day—held every year on the second Thursday of March. We, along with our international colleagues, celebrate this day that acknowledges our discipline's galaxy in the universe of medicine. Please turn the page for Dr. William Couser's editorial.

Jerry Yee, MD
Editor

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