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P43 Phossy jaw and inorganic phosphorus chemistry: a timely hypothesis

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Numerous cases of osteonecrosis of the jaw (ONJ) and more than 20 cases of cortical long bone fractures, chiefly of the subtrochanteric femur, have been reported recently in association with bisphosphonate (BP) therapy. It has been pointed out that ONJ strongly resembles the "phossy" jaw disease described in workers in 19th century white phosphorus (P) match factories. There is a striking resemblance as well between the clinical presentations of the modern long-bone fracture patients and fracture cases reported in 1899 in Manchester white P match workers. Four low-impact femoral fractures were described in 2 such workers in addition to 44 other cases summarized. Some of the cases included concomitant phossy jaw. Delayed healing resembling the modern cases was also documented. The author stated (in 1899) "...we have sufficient presumptive evidence to show that the osseous tissues of the body generally can be so altered by the prolonged action of phosphorus or its compounds as to render them less resistant to the application of external violence." The match-industry disease vanished with the substitution of red P for white. Elemental P occurs in several allotropes. The white, but not the red, spontaneously oxidizes in air to form P2O5, which may react with water to form several acids including pyrophosphoric acid (PPi). PPi would be present in inhaled white P smoke. Also, inhaled P2O5 could be hydrolyzed to PPi under physiologic conditions. Either thus could raise the serum concentration of PPi in the chronically-exposed individual. PPi is elevated in children with congenital hypophosphatasia, which is associated with disorders in the function of the

cortical alveolar bone and fragility fractures of the femur and metatarsals. The cortical alveolar bone has been suggested to be the originating locus in bisphosphonate-associated osteonecrosis of the jaw. BPs were originally chosen as potential pharmacologic analogs of PPi, because the latter had been found to decrease hydroxyapatite (HAP) solubility. The central P-O-P group was replaced by PC(R2)-P, conveying resistance to hydrolysis. After binding to bone under active osteoclasts, the commonly-prescribed nitrogen-containing BPs are ingested and inhibit osteoclast farnesyl pyrophosphate synthase. The ultimately resulting cellular changes lead to reduced bone remodeling activation. The hypothesis advanced is that the etiological agent of the match industry diseases of jaw necrosis and fragility fractures was PPi. This proposition is based upon the remarkable analogy between the clinical presentations in the problems associated with the match industry and the modern BP drugs and upon the fact that the two putative etiological agents share similar structural and HAP binding properties.

Disclosures: W.B. Hinshaw, Eli Lilly & Company 8; MDL- 1760 Committee 5.

