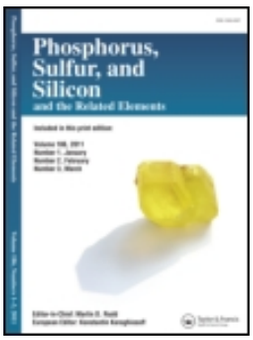

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RECOGNITION OF THE CAUSATIVE AGENT OF "PHOSSY JAW" AND "FRAGILE FEMUR" IN FUMES ARISING FROM WHITE PHOSPHORUS

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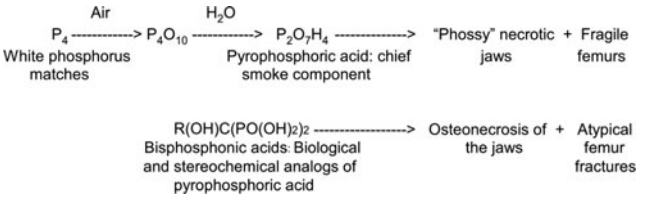
GRAPHICAL ABSTRACT



Abstract *Exposure to the fumes and smoke from white phosphorus pastes in the strike-anywhere match industry was associated, in the latter half of the 19th century, with a low incidence of necrotic lesions of the jaw bones and/or a fragility of the mid-femur occasioning fractures after minor trauma. Hundreds of cases were reported in many countries. The plight of these workers was the subject of international social pressure eventually leading to the prohibition of the matches. The reappearance in the early 21st century of two similar maladies associated with bisphosphonic acid (BP) medications led us to investigate the potential connection between these two pairs of debilitating effects. The BP molecules were chosen for development beginning in the early 1970s as pharmacologically satisfactory analogs of a simple inorganic phosphorus compound, pyrophosphoric acid, which had been found to exert an inhibitory effect on bone dissolution in vitro. These BPs inhibited bone loss in vivo. Independently, chemical analyses published in the mid-1980s demonstrated that the original small inorganic phosphorus model molecule was the most prevalent substance in the complex fumes and smoke associated with the pair of legacy diseases, thus persuasively connecting it, mediated by a common biological mechanism, to the modern drug side-effects.*

Keywords Phossy jaw; white phosphorus; osteonecrosis of the jaws; atypical femur fractures; bisphosphonates; pyrophosphoric acid

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Dedicated to Professor Robert R. Holmes in recognition of his pioneering research on phosphorus chemistry and his leadership in the field as Editor for many years of this Journal.

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EXPOSURE TO WHITE PHOSPHORUS FUMES AND BISPHOSPHONATE MEDICATIONS

Elemental phosphorus acquired considerable notoriety between 1830 and 1900 when the white allotrope was being used in strike-anywhere "Lucifer" match manufacture. Two very debilitating bone diseases occurred among the workers in this industry. These were a purulent and often fatal degeneration of portions of the jaws (popularly known as *phossy jaw*) and a susceptibility to low-impact fractures of the femoral shaft (styled *fragilitas ossium* at the time, an outdated and non-specific term). The victims were mostly young, working under conditions of exposure to the visible fumes arising from a hot paste containing white phosphorus (WP) into which wooden sticks were dipped, or involved in the boxing of the cooled matches where many small conflagrations were commonplace.[1] Ultimately white phosphorus (also known as yellow phosphorus) was banned from use in matches and replaced by the much less reactive red allotrope. A widespread assumption was prevalent that the WP itself was the cause of the diseases, leading to the coining of the name "phossy jaw." A comprehensive review of this industrial problem and the social response leading to its elimination has been authored by John Emsley.[2] However, there is now solid analytical chemical evidence[3] that there is virtually no elemental phosphorus in the plume which is formed by very rapid chemical changes of the element by oxidation–hydrolysis. Up to the present, except for our limited preliminary descriptions[4,5] no satisfactory and complete explanation, based on sound principles of phosphorus chemistry and experimental data, has been devised to account for this unusual toxic effect. A speculation has been published in the dental literature[6] in which the author rightly attempts to assign a chemical basis to the toxicity, but his explanation founders on the insupportable postulation of reactions which are unknown to modern chemistry including the synthesis of the carbon–phosphorus bond in methylene bisphosphonic acid in the human victims.

For many years no other low molecular weight organic chemical was known that caused jaw disease and femur fragility. The unique legacy diseases received little attention after Lucifer match production was forbidden. Workers in factories manufacturing WP or using it in fireworks or for military purposes were noted to occasionally suffer the same problems,[7,8] but these occurrences became very rare. However, in 2003, reports began to appear in the medical literature that a small percentage of persons taking certain C-substituted bisphosphonates (BPs) – derivatives of $H_2C(PO(OH)_2)_2$ – for bone therapy developed osteonecrotic lesions of the jaws,[9] and the similarity to phossy jaw was recognized.[10] Around the same time, reports appeared linking BPs to low-impact fractures of the subtrochanteric femur.[11] This provided us[†] with a significant clue to the identity of the chemical agent causing the legacy diseases. At the present time, the only other chemicals known to cause one or both of these bone problems are two high molecular weight proteins (antibodies) used in medicine. These compounds, which do not contain phosphorus, are denosumab[12] (M.W. 144,720) and bevacizumab[13] (M.W. 149,000). The mechanism of action of the first of these antibodies induces the same biologic change as the BPs, albeit by interference in a different step of the initiation of bone self-repair.[14] The mechanism of action of the second antibody differs qualitatively although the specific biologic change it induces has also been detected in association with the BPs.[15]

[†]Correspondence between WBH and LDQ beginning January 18, 2007.

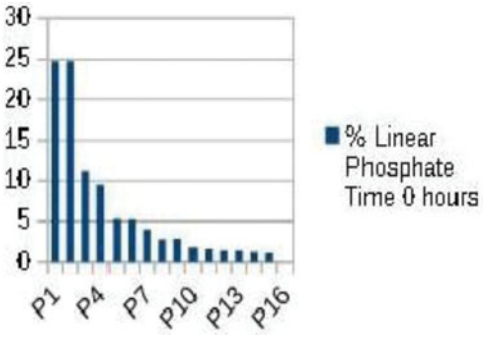

Figure 1 Initial composition of white phosphorus smoke.

THE ORIGINAL OBSERVATIONS ON PHOSSY JAW AND FRAGILE FEMUR

In 1899[16] and 1901,[17] the British physician William Dearden published his closely reasoned opinions as to the cause of the two industrial maladies described above. These problems had haunted the industry for more than 50 yr and had been the subject of extensive governmental investigations[18] and much public outcry.[19] In these papers, coming near the end of the era of the diseases, Dearden attempted to assign a specific chemical causation. He concluded that the diseases were possibly caused by the inhalation of "fumes of the lower oxide of phosphorus." He based this opinion on observations made by others[1] that workers exposed to the "fresher" cloud resulting from the large-scale mixing of the paste or small nearby conflagrations suffered a higher incidence of the diseases than those whose exposure was less immediate. Both of these exposures were common in the industry. The "fresher" plume was *assumed,* by some contemporary Victorian chemists, to hold a greater percentage of the more reactive (and thus posited to be more toxic) P(III)oxide (P_4O_6) compared to the "less reactive" P(V)oxide (P_4O_{10}). No reliable measurements of the actual chemical content of the aerosol resulting from the oxidation of WP in moist air were published until almost a century later, but when this was done, the new cloud did indeed prove to contain more of a toxic product in comparison to the older cloud, confirming the temporal impression in the legacy cases, if not the postulated reason for the differential effect. US Army studies of the contents of the smoke generated by exposure of felt saturated with WP to humid air are shown at several intervals (Figures 1–4 and Table 1) starting with ignition (adapted from Spanggord et al.[20]).

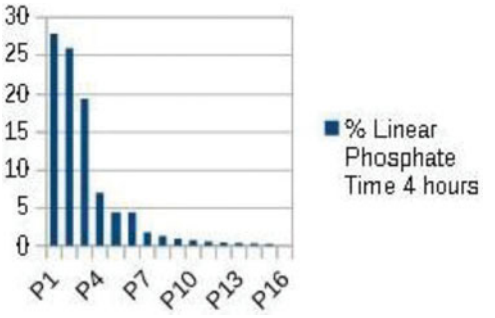

Figure 2 Composition of white phosphorus smoke after 4 hours.

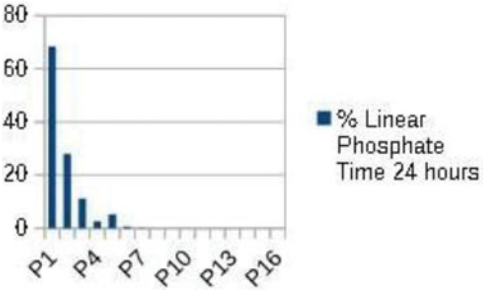

Figure 3 Composition of white phosphorus smoke after 24 hours.

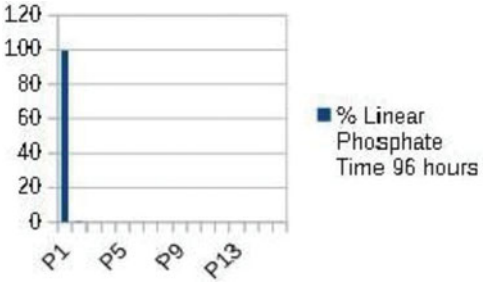

Figure 4 Composition of white phosphorus smoke after 96 hours.

A clue to the identity of the toxic agent can be found in this analysis. This will be made clear below.

Dearden also reported that comparison of the phosphorus content of bones from an affected and a normal individual differed in crude phosphorus content. He advanced the opinion that "the formation of a [new] compound of phosphorus in bone is a most reasonable

Table 1 Quantitative analysis of white phosphorus smoke over time

Linear Phosphate	% GC curve area @ 0 h	@ 4 h	@ 24 h	@ 96 h
Phosphate	24.77	27.83	68.52	99.54
Pyrophosphate	24.82	25.94	28.00	0.46
Triphosphate	11.14	19.44	2.61	
Tetraphosphate	9.49	7.01	0.64	
P5	5.22	4.42	0.23	
P6	5.13	4.23		
P7	4.05	1.78		
P8	2.83	1.29		
P9	2.89	0.92		
P10	1.87	0.76		
P11	1.65	0.55		
P12	1.50	0.43		
P13	1.46	0.33		
P14	1.27	0.29		
P15	1.19	0.24		
P16	0.00			

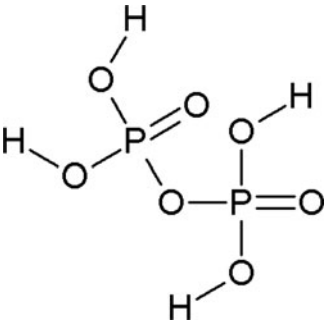

Figure 5 Pyrophosphoric acid.

explanation" of the industrial diseases. He pointed out that the jaw problem could possibly result from a local effect on the teeth or gingiva but that no local effect could very well explain the weakness of the femur. The two conditions were sometimes observed in the same individual. The intense public concern mentioned above eventually resulted in legislation prohibiting the production or sale of the WP matches, finalized at various dates in different countries around the turn of the century. Even though these industrial diseases affected only a miniscule portion of the population, and an impoverished and disenfranchised one at that, after 1880 the increasing public indignation convinced the authorities to outlaw these matches, thus effectively eliminating new cases of phossy jaw and fragile femur and resulting in rapid acceptance of satisfactory alternatives to the WP match after some 50 yr of stubborn resistance from the profitable industry and untold misery among the factory workers.

THE DISCOVERY OF THE USE OF BISPHOSPHONATES FOR BONE DISEASE

Beginning in the late 1950s, the Swiss physiologist Herbert Fleisch developed an interest in the impact of salts of pyrophosphoric acid (PPi) on bone metabolism. He first noted[21] the physical chemical influence of PPi (Figures 5 and 6) in buffered solutions on the solubility and crystallization of "hydroxyapatite," the modified calcium phosphate that approximates the mineral content of bone. He then discovered[22] that bisphosphonic acid

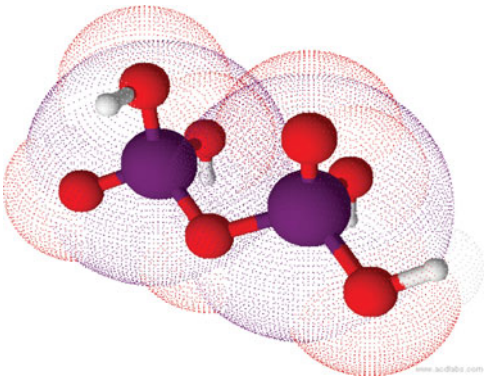

Figure 6 Pyrophosphoric acid.

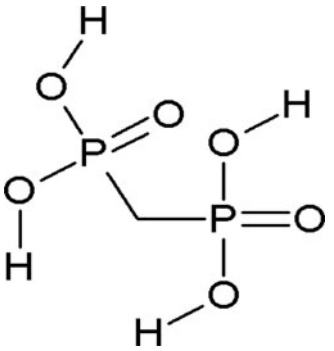

Figure 7 Methylene bisphosphonic acid.

salts (Figures 7 and 8, structural and stereochemical analogs of PPi with carbon replacing the central oxygen atom) had the same effect as PPi both in vitro as initially noted and as well as in living animals. The analogous shape of the molecules was deemed responsible for this similar effect. Fleisch was able to show[22] that the mechanism of the observed results was an inhibition of bone "resorption" (described below). He concluded that such an inhibition could prevent the age-related bone loss resulting in increasing bone fragility. He promoted the use of these compounds to reverse the lost bone mass occurring in "osteoporosis."

Fleisch and his coworkers evidently became convinced[23] that PPi salts administered in vivo were rapidly lost by hydrolysis and thereafter concentrated on the BPs which in vivo have non-hydrolyzable phosphorus–carbon bonds. The structures of the most important BPs used in osteoporosis therapy are shown in Figure 9. All of these have nitrogen-substituted side-chains, but this substitution is not necessary for antiresorptive (see below) activity, as shown by the similar activity seen with the dichloro derivative clodronate: $Cl_2C(PO(OH)_2)_2$.

It is of note, in the context of this paper, that Fleisch described[24] the induction by BPs, in rodents, of a state resembling the genetic anomaly of osteopetrosis,[25,26] a disease characterized by brittle bones and femur fractures due to an inherited defect in the resorption process. It is also noteworthy that Fleisch described[27] the induction of radiographic condensations near the long-bone metaphyses in rodents, a phenomenon which will be shown below to resemble lesions found in the match workers 70 yr earlier.

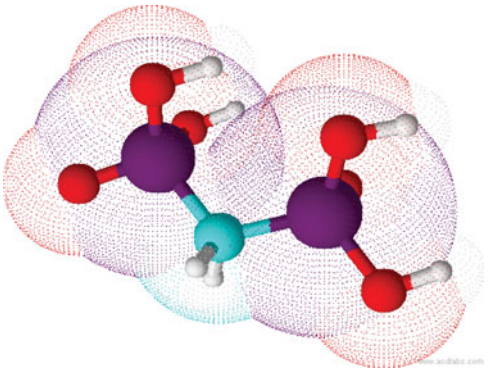

Figure 8 Methylene bisphosphonic acid.

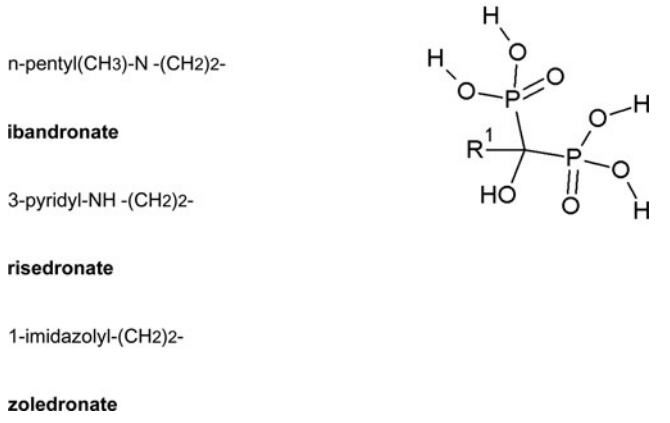

Figure 9 Bisphosphonates (acid forms) approved for osteoporosis in the United States.

THE COMMON BIOLOGICAL PROPERTIES OF PPi AND BPs

An extensive discussion of the mechanisms of the many stages of bone metabolism is beyond the scope of this paper; however, a summary of the basic process of skeletal self-maintenance will be offered to give our conclusions a proper context, to be discussed, connecting the BP observations to the recognition of the chemical cause of phossy jaw and fragile femur. Bone is made up of living cells and structural proteins as well as an intercalated mineral phase. Its metabolic activity[28] results in periodic replacement of small "packets" and "osteons" where the cell-mediated removal of older, i.e., replaced in the relatively distant past, and damaged bone in a *resorption phase* is followed by the cell-mediated replacement of the removed tissue in a formation phase, followed eventually by calcification of the new organic framework. An age-related quantitative excess of the resorptive over the formative phase results in a net loss of bone mass and a potential increase in fracture risk. When this occurs, the condition known as "osteoporosis" may lead to fragility fractures. Fleisch and his successors found that the BPs inhibited the resorption phase (thus are "antiresorptive") and hypothesized that this would prevent such bone loss.

The American physiologist Harold Rasmussen demonstrated contemporaneously with Fleisch's work that the latter's impression that PPi salts could not survive hydrolysis in vivo long enough to effect inhibition of resorption was erroneous. Rasmussen described[29] physiological effects on bone metabolism identical to those caused by the BPs when buffered PPi was infused intravenously under carefully controlled conditions. This 1971 work, using a parenteral rather than an oral route of administration, provides a critical clue in the challenge of rationalizing what was happening to the 19th century match factory workers. Bypassing the gastric acidic milieu allowed PPi to function like the BPs. Rasmussen was seemingly ignored by the rapidly enlarging research community

following the lead of Fleisch, even though some contemporaneous work from his lab[30] was consistent with Rasmussen's discovery. Exemplary of this expanding interest was the discovery of a BP not initially studied by Fleisch but destined to become one of the most popular of the developed agents. In 1978, Martin Kabachnik in Russia described[31] the synthesis of 4-amino-1-hydroxybutane-1,1-bisphosphonic acid, which became known as alendronic acid (see Figure 9). In 1982, the Italian pharmaceutical firm Instituto Gentili patented[32] the use of this compound as an inhibitor of bone resorption. The inspiration for the Italian evaluation of this compound doubtless lay in the widely published work of Fleisch, describing very similar molecules. The Gentili use patent claimed a property which prevented any imbalance in bone remodeling. Alendronic acid, which was later commercialized as Fosamax™, is thus another carbon analog chosen to mimic the physiological effect of PPi, the reason for the interest and exploitation of the BPs by Herbert Fleisch.

As already noted, the US Army undertook the analysis of the flume released from WP exposed under defined conditions to moist air. The cloud released was used by the military as a combat obscurant and likely resembled the drifting fumes and smoke which has been described as existing in certain critical areas of the Victorian era match factories. Two independent Army-supported analyses were published.[3,20] These agree that there is no detectable persistence of the P(III)oxide (P_4O_6). The early speculation that this compound might be responsible for the industrial diseases can be discarded. The amount of the starting WP in the initial aerosol was estimated to be at most a few parts per billion.[3] This eliminates the second legacy theory that the industrial diseases were due directly to exposure to elemental WP. Physical contact in the factories with WP, recognized as a deadly poison, was scrupulously avoided, but inhalation of the fumes and smoke was not so easily prevented. In addition, the analyses found that no P(V)oxide (P_4O_{10}) was present in the initial aerosol. The smoke mostly consisted of linear polyphosphosphoric and orthophosphoric acids (Pi) and a few very minor amounts of cyclic metapolyphosphoric moieties. Indeed the P(V)oxide, after rapid reaction with water, must have been the precursor of these entities. Traces of phosphorous and hypophosphorus acids were also detected. But the most prevalent constituent of the initial flume was the penultimate hydrolysis product of the P(V)oxide, pyrophosphoric acid, the very compound whose physical–chemical effects had been intentionally mimicked by the BP salts (Fleisch) and whose physiological bone effects had been demonstrated to be equivalent as well (Rasmussen). The percentages of PPi versus Pi in the initial smoke in the two studies were 26.6% versus 23.8% and 24.82% versus 24.77%. The second Army analysis shows that with the passage of time under ordinary atmospheric conditions, the amount of PPi in the flume was approximately constant as the longer linear polyphosphates were hydrolyzed to shorter chains, but eventually hydrolysis converted all of it to Pi (see bar chart summations in Section 1). By 96 h, PPi had become almost undetectable. However, these analyses identify the largest constituent of the early cloud (which was associated with a higher incidence of the diseases than the older cloud). That constituent was pyrophosphoric acid.

The Rasmussen work proved that PPi at physiologic pH infused intravenously persists long enough to induce suppression of bone resorption, but to have a similar effect in the case of the legacy diseases, chronic pulmonary absorption (another parenteral route) of the PPi from the fumes and smoke would have been required. There is some evidence suggesting that this is possible. The compound is water soluble and stable at physiologic pH as well as in the highly disbursed acidic aerosol. Fleisch[33] found that the 99mTc–Sn–PPi complex

(a radiopharmaceutical used for bone imaging since 1972) injected in rats was rapidly taken up into bone and labeled PPi behaved similarly. Pulmonary uptake following inhaled aerosols of the same complex in humans has been studied by scintigraphy and blood aliquot analysis. It was shown[34] that 50% was cleared from the lungs at 3 h; 3.9% of the inhaled marker already appeared in the blood at 1 h. The clearance of this complex from lung into blood and of the complex as well as PPi alone from blood into bone (as demonstrated by Fleisch) implies that a transfer of inhaled PPi from the lungs to bone is possible.

The last part of this logical progression toward understanding the cause of the legacy diseases is the consideration of the nature of the two major side effects reported by the modern BP medications mentioned in our first paragraph. These are, insofar as can be ascertained at this long remove in time, the same two described by Dearden more than a century earlier. As noted, the association, with BP treatment, of a necrotic lesion of the jaws, now known as "osteonecrosis of the jaws" (ONJ) was first reported[9] in 2003. Subtrocanteric (femoral shaft) fractures in similar circumstances were reported[11] the same year. Subsequently cases of both effects in the same individual have been seen and thousands of individual incidents of the two problems have been described and summarized[35,36,37]. Long-term morbidity has been documented.[38] The relationship of these two side-effects to the BP drugs has been, to say the least, contentious. However, we believe that the remarkable parallel association of the two pairs of diseases, the legacy pair resulting almost certainly from exposure to PPi, a known inhibitor of the resorption-phase bone self-maintenance, and the modern pair being the side-effects associated with compounds modeled on and sharing the demonstrated physical and physiologic properties of PPi, provides a convincing inductive argument for a common etiology. Thus, we are led to the conclusion that the chemical agent causing phossy jaw and fractured femurs among the match workers of Victorian times on prolonged exposure to the fumes arising from white phosphorus was pyrophosphoric acid. This conclusion requires experimental support for the concept that both PPi and BPs can bond to bone. Dearden had speculated that components (unspecified) of the vapor arising from phosphorus in the Victorian match industry could bond to bone, and offered a single comparative quantitative analysis of affected and unaffected bone as evidence. However, data from the very old radiological literature provide additional and quite striking support for this conclusion. In a paper published just five years after Roentgen first demonstrated the ability to visualize the skeleton by X-rays, the effects on the skeleton of workers undergoing prolonged exposure to the factory environment of the phosphorus match industry were described[39] in the German medical literature. While standardized nomenclature was undeveloped at the time, it was reported (in German) "One [has] the impression that the longer-lasting the effect of the phosphorus vapor at match work on the growth of bone.., [the more] this leads to compressions [dark lines] near the [ends] of the [long] bones." Since that original observation in the match victims, this same finding has been reported, not only in Fleisch's osteopetrosis model mentioned above, but also[40] for BPs in circumstances of excess human exposure to the drugs as well as in experiments[41] with animal models.

A more direct proof of chemical bonding to bone by the BPs supports Dearden's original hypothesis that components of the phosphorus vapor combined chemically with bone. ^{31}P-NMR studies reported by Oldfield[42] have demonstrated that one of the phosphonic acid arms in the bisphosphonates is capable of displacing a phosphate group from the surface of hydroxyapatite in human bone thus binding to the bone mineral. This has long been assumed to be the case[43] although structural details had been missing.

Enzyme inhibition studies have also shown similarity of behavior of BPs and PPi. In vivo, the antiresorptive effect of small doses of bisphosphonate drugs is markedly enhanced by local concentration due to affinity for the exposed hydroxyapatite undergoing remodeling.[44] The inhibition depends on the osteoclast (resorbing cells) taking up the concentrated drug in the process of removing the bone where the BP has accumulated. Inside the cell, the BP has access to the mevalonate cycle enzyme farnesyl pyrophosphate synthase (FPPS), whose inhibition by the drug in vivo halts the resorption process.[45] Both the BPs and pyrophosphate inhibit this enzyme in vitro,[46] PPi demonstrating weaker but parallel activity with bisphosphonates and thus also supporting our conclusion that the agent causing phossy jaw among workers exposed to fumes while processing WP is pyrophosphoric acid.

In the late 1990s, the inventor of this entire class of medicinal chemicals, Herbert Fleisch, on considering the full implications of his work, stated[47] "The effect of the bisphosphonates upon the mechanical properties of the skeleton has been addressed only recently. This issue is important since long lasting, strong inhibition of bone resorption can lead to increased bone fragility and, therefore, to fractures caused by the inability to replace old bone by young bone . . . ." The same statement would apply to long-term inhibition of bone resorption following chronic inhalation of PPi, a circumstance of the side-effect plagued Victorian WP match industry.

CONCLUSIONS

In summary, we have found that the scientific literature contains sufficient information to reasonably conclude that the legacy diseases of phossy jaw and femur fragility were caused by chronic inhalation of PPi suspended in the fumes and smoke emanating from WP. There is no other demonstrated candidate for causation of these diseases present in the vapors. (Fleisch did publish[48] several papers attempting to evaluate the skeletal impact of mixed polyphosphates in vivo, but the published results were inconclusive, the mixtures were poorly defined, and the work was never followed up. PPi is an inhibitor of FPPS and a common entity in mammalian metabolism. Even if the polyphosphates were to share some of its properties, it seems likely that this would only increase the potency of the inhaled flume. In any case, the polyacids were never considered as models for the development of medicinal entities.) The most important fact leading to our conclusion remains the modern finding of a pair of virtually identical diseases noted after chronic treatment with C-substituted BP moieties, whose biological activity was discovered because the BPs produced physiologic changes that had been observed with PPi. Without this latter basis, the candidacy of PPi as the causation of the legacy diseases would likely have gone unnoticed. However, the dual chains of evidence arriving at the same end results also argue persuasively that the disputed causation of modern diseases of ONJ and femur fragility is directly attributable to the BP drugs that are associated with them.

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