Uncovering the Cause of “Phossy Jaw”
Circa 1858 to 1906: Oral and Maxillofacial Surgery Closed Case Files—Case Closed

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The infamous “phossy jaw” that created an epidemic of exposed bone osteonecrosis exclusively in the jaws began around 1858 and continued until 1906, with only a few cases appearing since that time. This epidemic of osteonecrosis produced pain, swelling, debilitation, and a reported mortality of 20% and was linked to “yellow phosphorous,” the key ingredient in “strike-anywhere” matches. In match-making factories, workers called “mixers,” “dippers,” and “boxers” were exposed to heated fumes containing this compound. Related to the duration of exposure, many of these workers developed painful exposed bone in the mouth, whereas their office-based counterparts did not. The exposed bone and clinical course were eerily similar to what modern day oral and maxillofacial surgeons see due to bisphosphonates used to treat metastatic cancer deposits in bone or osteoporosis.

Although yellow phosphorus has a simple chemistry of \( \text{P}_4\text{O}_{10} \), when combined with \( \text{H}_2\text{O} \) and \( \text{CO}_2 \) from respiration and with common amino acids, such as lysine, bisphosphonates almost identical to alendronate (Fosamax; Novartis Pharmaceuticals, East Hanover, NJ) and pamidronate (Aredia; Novartis Pharmaceuticals) result. Forensic evidence directly points to conversion of the yellow phosphorus in patients with “phossy jaw” to potent amino bisphosphonates by natural chemical reactions in the human body. Thus, the cause of phossy jaw in the late 1800s was actually bisphosphonate-induced osteonecrosis of the jaws, long before clever modern pharmaceutical chemists synthesized bisphosphonates. Today’s bisphosphonate-induced osteonecrosis represents the second epidemic of “phossy jaw.” Case closed.

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The revelation in 2003 that modern intravenous and even oral bisphosphonate medications can produce exposed necrotic bone in the jaws drew immediate comparisons to the infamous and poorly understood “phossy jaw” phenomenon of the late nineteenth century and early twentieth century. Indeed, both entities are somehow linked to phosphorous or phosphate-containing compounds and lead to exposed necrotic bone in the jaws either spontaneously or after tooth extractions, readily become infected, fail to heal, respond poorly to debridement surgeries, and significantly disable many individuals. Given our current knowledge of phosphorus chemistry, the known mechanism by which bone remolds and renews itself, and the intracellular actions of bisphosphonates on known metabolic pathways, these 2 diseases, although separated by time and route of exposure, can be shown to be one and the same entity.

A Brief History of “Phossy Jaw”

The impetus for “phossy jaw” was the desire to create so-called “strike-anywhere” matches. In the pre-electricity and pre-incandescent light times of the middle 1800s, rural and city dwellers alike lit their kerosene lamps and fireplaces with either residual embers or flint and steel. There was an understandable demand for an easier and more convenient method to illuminate and heat households. In 1826, the first matches, popularly known as “lucifers,” were introduced. But these matches proved difficult to ignite and thus were not well accepted. Their ignition surface was a mixture of antimony sulfide and potassium chlorate in a binder known as “gum.” In 1832, it was discovered that the incorporation of yellow phos-
phorus (today called white phosphorus) produced an easy-to-light match that indeed could be ignited by striking it virtually anywhere. Today, we know that white phosphorous (P₄O₁₀) is an unstable form of phosphorus that ignites at much lower ignition temperatures than the more common red phosphorus, which in today's matches is incorporated into the rough surface of matchboxes for easier and more controlled ignition.¹

The "strike-anywhere" matches immediately gained popularity. They contained more yellow phosphorus than was absolutely required, however, and spontaneous ignition on shaking the box or leaving the box in a warm room or exposed to the sun resulted in numerous house fires. Nevertheless, the overwhelming convenience of lighting a fire anywhere and under almost all conditions created an enormous demand. Thus, a new industry was born. Nearly all countries quickly developed a matchmaking industry as part of the international industrial revolution of the nineteenth century. Ironically, in response to the house fires produced by the strike-anywhere matches, in 1855 Swedish scientists created a "safety match" that contained no yellow phosphorus and, based on what we know today, could possibly have prevented the epidemic of "phossy jaw" that was about to occur. Their simple creation used the original 1826 match head containing antimony sulphide and potassium chlorate and placed the more stable red phosphorus in the rough surface of the strike line on the side of the box, much as is done in today's matches. This "safety match" was later adapted and has persisted to modern times, but now is used less often due to the advent of the cigarette lighter and its many modifications. Due to the greater convenience offered by the strike-anywhere matches, the safety match was largely ignored. Match factories sprang up in every country, hiring workers for 10- to 15-hour workdays over large heated vats containing yellow phosphorus and emitting vapors that were breathed in by workers called "dippers," "mixers," and "boxers."

Detailed medical reports of a disease involving slow progression of exposed jaw bone began to appear as early as 1858.² One report noted an "ultimate outcome that was mutilating and miserable jaw suppuration associated with gradual deterioration of general health" (Fig 1).³ This and other reports added to the rumors already circulating about workers suffering in the match-making factories. The first detailed report, from France in 1858, identified 60 cases, of which half had died, some from suicide related to their jaw necrosis and unrelenting pain.⁴ This was followed by a historically significant publication by Simon in 1863 recounting the report of a Dr Bristowe to the British Parliament in 1862, as the medical officer of the Privy Council.⁵ Simon related Dr Bristowe's account of 61 cases of jaw necrosis, reporting that "typically a dull red area developed in the gum, usually in relation to an infected tooth. An indolent ulcer formed or following the extraction of a tooth, the socket refused to heal and soft tissue inflammation persisted. There was a relatively slow progressive extension with eventual separation of or sequestration which is classically described as porous and light in weight and presenting a worm-eaten appearance likened to pumice stone." To those clinicians familiar with today's bisphosphonate-induced osteonecrosis, this presentation, course, and outcome are eerily similar. Bristowe further noted that the dippers with the longer duration of exposure to the heated phosphorus vapors had the highest incidence of bone necrosis, that the bone necrosis developed only after years of working in the match factory, and that the lower jaw was more commonly affected than the upper jaw. These observations coincide with the dose-time relationships and the more common location of occurrence seen in today's bisphosphonate-induced osteonecrosis resulting from therapy with either intravenous or oral bisphosphonates.

A detailed report of a representative case described by Smith in 1865 further relates the extent, pain, frustration, and outcome of phossy jaw that surgeons of that era had to deal with.⁶ It can serve as a lesson for us today; here it is reproduced as written in 1865,
with images from cases of bisphosphonate-induced osteonecrosis interspersed, to underscore the similarity of the 2 entities. Smith reported that “the patient was a 35-year-old lucifer match maker who presented with great external swelling and in a debilitated state from inability to take solid food (Fig 2). Extending from ear to ear along the line of the jaw was a chain of ulcerated openings, from which there was profuse discharge and through any of which a probe could reach dead bone (Fig 3). Inside the mouth, the toothless alveolar process was seen bared of soft parts in its whole extent, the bone being rough and brownish-black (Fig 4). The gum gaped widely away from the dead jaw and had receded so as to leave it above the natural level of that bone (Fig 5), a probe could be passed easily either in front or behind the bone toward the sinuses in the neck. Under chloroform, the jaw was removed by dividing it at the symphysis and dragging the two halves out separately (Fig 6). Considerable force was required to detach the bone from its connections, but it was not necessary to make any use of the knife; the dead bone came away completely denuded of soft parts and without the slightest remnant of periosteum.”

Smith went on to report that this patient healed and was much improved but died 6 weeks later of an upper airway obstruction, after “imbibing freely of stimulants.” The jaw specimen from this case is currently on display in the Odontologic Museum, Royal College of Surgeons in London.

This account from 1865 and the images from some current bisphosphonate-induced osteonecrosis cases indeed underscores the clinical similarities of the 2 entities. It should humble the reader to realize that this major procedure described in the 1865 report was accomplished by a surgeon with no oral and maxillofacial surgery training, without intubation,
without cautery, and without antibiotics. The outcome of death due to upper respiratory obstruction is not surprising, considering that tracheostomy was not commonplace at that time and was not performed. Such extensive jaw involvement is sometimes seen in today’s bisphosphonate-induced osteonecrosis and is the main indication for resective surgery. Despite modern anesthesia, antibiotic support, and the specific training of oral and maxillofacial surgeons, the risks associated with major surgery during and after the procedure remain.

From 1863 to 1899, numerous additional cases of “phossy jaw” were reported, which generated great political and public awareness. Finland banned the use of yellow phosphorus matches in 1872, and Denmark followed suit in 1874. However, like many political issues, controversy, activist organizations, and accusations of cover-up emerged. In an 1899 report to the British Parliament, the Chief Inspector of Factories stated that “certain cases of phosphorus necrosis had been intentionally concealed and others had escaped records.” In 1890, the founder of the Salvation Army, General Booth, and assistant James Barker began an activist campaign to expose the dangers in the match-making industry. They described extensive areas of exposed bone and severe pain and pointed out that many of these workers were young girls and women. In addition, James Barker was noted to take people to visit sufferers of “phossy jaw” and to make a dramatic showing of turning out the room light to reveal the glow emitting from the exposed bone in the mouth.

By the early 1900s, the link between “phossy jaw” and match-making factories was well established and publicly and politically unacceptable. Political action was taken in 1906 at the Berne Convention held in Berne, Switzerland, with a ban on strike-anywhere matches. All countries accepted and signed the Berne Convention ban with one notable exception: the United States. Under the rationale of free and unrestricted trade, the United States refused to accept the ban. It was not until 1931 that yellow phosphorus-containing matches disappeared in the United States, when a high tax on these matches made them cost-prohibitive.

Even with the Berne Convention ban of 1906 and the conversion to safety matches without yellow phosphorus, sporadic cases of “phossy jaw” continued to appear in the literature until recent times. All of the cases reported since 1906 also were associated with exposure to yellow phosphorus, mostly in munitions and fireworks factories, which still used yellow phosphorus. Needless to say, the number of cases since 1906 is dwarfed by the epidemic number occurring between 1858 and 1906.

The Forensic Link Between “Phossy Jaw” and Bisphosphonate-Induced Osteonecrosis

Although the clinical development and appearance of exposed necrotic bone exclusively in the jaws and favoring the lower jaw, its persistent and slow progression and tendency to become infected, as well as its association with phosphorus compounds suggest a common cause in “phossy jaw” and bisphosphonate-induced osteonecrosis, they are hardly proof. Forensic proof comes from an understanding of bisphosphonate chemistry, its mechanism of action, and the chemistry of yellow (white) phosphorus conversion in the body.
Basic Bisphosphonate Chemistry and Mechanism of Action

The basic chemistry of bisphosphonates is shown in Figure 7. It is known that the backbone carbon renders the molecule incapable of breakdown by hydrolysis and binds it tightly to the hydroxyapatite crystals in bone. The hydroxyl group (OH) on the backbone carbon increases the bond strength to hydroxyapatite and explains the bisphosphonates’ 10-year half-life in bone. This tight bonding to bone can be released only on acid-mediated bone resorption, making the osteoclast the one and only cell to ingest the drug and identifying the osteoclast as the cell targeted by the bisphosphonate. The second bonding site on the backbone carbon is referred to as the R₂ group. Substitutions in this position relate to potency; R₂ substitutions with amide or cyclic configurations containing nitrogen are known to add potency, and to date, only nitrogen-containing bisphosphonates have caused osteonecrosis of the jaws.

The importance of a dysfunctional or absent osteoclast population lies in its affect on bone turnover. Despite its physical hardeners, bone is a dynamic living tissue that must renew itself, like skin. If it does not, then it literally becomes old and dies (osteonecrosis). Bone renewal is initiated by the very cells that bisphosphonate toxicity targets: osteoclasts. When an osteoclast resorbs bone, it releases bone morphogenetic protein (BMP) and insulin-like growth factors (ILGs) 1 and 2, which were originally placed into the noncollagenous organic matrix of bone by the osteoblast. The released BMP, ILG₁, and ILG₂ then direct the migration, differentiation, and osteoid production of new bone from local and circulating stem cells. The histological composite of osteoclasts resorbing bone with a trail of osteoblasts reforming bone is called a bone metabolic unit (BMU) (Fig 8).
Thus, the unique chemistry of bisphosphonates leads them to irreversibly bind to bone, being ingested only by osteoclasts, and literally poison the osteoclasts so as to reduce or eliminate bone turnover. This, coupled with the fact that alveolar bone in the mandible and maxilla is known to turnover much faster than long bones, explains why the jaws are the target of this toxicity and that bisphosphonates are the sole culprits. But how does yellow phosphorus become a bisphosphonate?

**Forensic Science of Yellow Phosphorus**

The precursor compound of bisphosphonates is pyrophosphate, exemplified by 99-technetium methylene diphosphonate (99TcMDP), the common radioisotope in bone scans today. Scans of pathologies known for active bone formation or remodeling show a dramatically increased uptake of this molecule in bone, attesting to the affinity of diphosphonates for sites of active bone turnover (Fig 9). The pyrophosphate molecule, $P_2H_4O_7$, is derived from the basic molecular structures of yellow phosphorus, $P_4O_{10}$ (Fig 10), by the addition of 2 $H_2O$ molecules. But pyrophosphates are completely water-soluble, non-toxic, and 100% metabolized by hydrolysis. They also are rapidly eliminated in the urine due to their high water solubility. Pyrophosphates also are called diphosphonates because of the 2 phosphate groups attached to the backbone oxygen atom in the molecule, and they become bisphosphonates only when a carbon atom is substituted for the oxygen (Fig 7). But when this occurs (or is created by a clever pharmaceutical chemist), the properties of the molecule change dramatically. As discussed previously, the backbone carbon makes hydrolysis impossible, and thus the molecule cannot be broken down and eliminated. Moreover, the carbon backbone provides a tight binding to the hydroxyapatite crystals in bone.

With substitution of the hydrogen on the backbone carbon position by a hydroxyl group (OH), this binding becomes virtually irreversible.

This chemistry explains the long half-life in bone of all of the bisphosphonates, particularly pamidronate (Aredia; Novartis Pharmaceuticals, East Hanover, NJ), zoledronate (Zometa; Novartis Pharmaceuticals), resldronate (Actonel; Procter and Gamble Pharmaceuticals, Cincinnati, OH), and ibandronate (Boniva; Roche Laboratories, Nutley, NJ), all of which have this hydroxyl substitution on the backbone carbon. This carbon backbone can come from CO$_2$ or carbonic acid (H$_2$CO$_3$), both of which are abundant in the tracheobronchial tree and lungs. It also may be transferred as a single carbon unit through the known 7-step process starting with N$^5$ methyl tetrahydrofolate (THF) and dihydrofolate reductase. Therefore, the basic pyrophosphate molecule ($P_2H_4O_7$) combines with CO$_2$ and $H_2O$ or carbonic acid through the well-known equation ($CO_2 + H_2O = H_2CO_3$) or, more likely, from the known human biologic method of single carbon unit transfers that produce the active co-enzyme form of THF. In this manner, a first-generation bisphosphonate ($P_2H_4CO_7$) forms (Fig 11).

This first-generation bisphosphonate created from simple yellow phosphorus ($P_4O_{10}$), $H_2O$, and either CO$_2$ or THF single carbon transfers has the carbon backbone and its attached hydroxyl group to confer a long half-life and complete resistance to hydrolytic breakdown, but not potency, and cannot induce osteonecrosis. The potency of today’s pharmaceutical bisphosphonates is related to the stereochemistry of the second bonding site on the backbone carbon, the $R_2$ group. In fact, the first and least potent of the synthetic bisphosphonates, etidronate (Didronel; Procter and Gamble Pharmaceuticals), is a non-nitrogen-containing bisphosphonate, as is tiludronate (Skelid; Sanofi-Aventis, Bridgewater, NJ). Neither of these agents has been known to produce bisphosphonate-induced osteonecrosis.

The critical nitrogen can come from ammonia (NH$_3$) or, more likely, from amino acids, such as...
lysine, all of which are ubiquitous in cellular metabolism. The nitrogen on the R₂ position arising from ammonia produces a nonchained simple natural aminobisphosphonate (Fig 12) similar, but not identical, to the synthesized therapeutic bisphosphonates that cause osteonecrosis of the jaws. But its properties are the same as those of any nitrogen-containing bisphosphonate, and it can be expected to interrupt the mevalonate branch pathway of the osteoclast and lead to suppression of bone turnover and osteonecrosis. In this case, however, the nitrogen most likely arose from amino acids such as lysine, which reacted directly with the yellow phosphorous to produce a carbon-amide chain on the R₂ position of the backbone carbon, creating a very potent aminobisphosphonate almost identical to alendronate (Fosamax) and pamidronate (Aredia) (Figs 12, 13).

To reconstruct the “scene of the crime,” the forensic scenario for the unsuspecting and unfortunate strike-anywhere match factory worker begins with long hours, working over heated vats emitting vapors containing the unstable yellow phosphorous, and the other substandard working conditions known to exist in that era, including unheated and unventilated rooms, lack of sanitation, few if any work breaks, and lack of medical and dental examinations and care. Communicable diseases such as tuberculosis, cholera, and typhoid are the possible comorbidities of that era, much like chemotherapy, steroids, and various dental diseases and surgeries represent the comorbidities of the current era. The unsuspecting workers breathed in the P₂O₁₀ vapors, which then passed through their alveolar membranes in the lungs and reacted with the CO₂, H₂O, and THF pathways in the tissues to produce a simple bisphosphonate. This simple bisphosphonate may have circulated systemically to combine with either ammonia to produce a potent nitrogen-containing bisphosphonate or directly combined with any of numerous common amino acids, such as lysine, to produce an even more potent aminobisphosphonate. This nitrogen-containing bisphosphonate circulated just as today’s oral nitrogen-containing bisphosphonates or the intravenous nitrogen-containing bisphosphonates circulate, with absorption into the bony matrix at all skeletal sites. Daily repetition of this scenario led to an accumulation of toxic levels in skeletal tissues over the years, with the jaws particularly vulnerable. Thus, the strike-anywhere match factory workers of the mid to late 1800s actually developed bisphosphonate-induced osteonecrosis of the jaws, in many cases severe, with complete mandibular sloughing and/or death, due to longer and

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**FIGURE 11.** Pyrophosphates can be converted to a bisphosphonate intermediate by combining with carbonic acid or more likely by the well known one carbon biochemical transfer processes of tetrahydrofolate (THF).

**FIGURE 12.** The first generation bisphosphonate intermediate can combine with common cellular amino acids such as lysine to become a potent nitrogen-containing bisphosphonate.

more insidious exposure, the absence of antibiotic therapy, and the lack of medical and dental care, as well as the comorbidities from the various infectious disease that were rampant during that era. Their own tissues synthesized potent nitrogen-containing bisphosphonates more than a century before the pharmaceutical chemists of today created the same effect and thereby produced osteonecrosis in another epidemic pattern in another generation of unsuspecting individuals. “Phossy jaw” is bisphosphonate-induced osteonecrosis, and bisphosphonate-induced osteonecrosis is “phossy jaw.” Case closed.

References

FIGURE 13. The nitrogen-containing bisphosphonate originating from yellow phosphorous (phossy jaw bisphosphonate) is similar to pamidronate (Aredia) and alendronate (Fosamax) in its chemical formation and structure.

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