

Calcium orthophosphates and human beings

A historical perspective from the 1770s until 1940

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The historical development of a scientific knowledge on calcium orthophosphates from the 1770s until 1940 is described. Many forgotten and poorly known historical facts and approaches have been extracted from old publications and then they have been analyzed, systematized and reconsidered from the modern point of view. The chosen time scale starts with the earliest available studies of 1770s (to the best of my findings, calcium orthophosphates had been unknown before), passes through the entire 19th century and finishes in 1940, because since then the amount of publications on calcium orthophosphates rapidly increases and the subject becomes too broad. Furthermore, since publications of the second half of the 20th century are easily accessible, a substantial amount of them have already been reviewed by other researchers. The reported historical findings clearly demonstrate that the substantial amount of the scientific facts and experimental approaches have been known for very many decades and, in fact, the considerable quantity of relatively recent investigations on calcium orthophosphates is just either a further development of the earlier studies or a rediscovery of the already forgotten knowledge.

Introduction

By virtue of abundance in the nature and presence in the living organisms, calcium apatites[†] and other calcium orthophosphates (Table 1) appear to be the chemical compounds of a special interest in many fields of science, including geology, chemistry, biology and medicine.^{1,2} As follows from the designation, calcium orthophosphates contain both calcium (Ca, atomic number 20) and phosphorus (P, atomic number 15) as the major constituents. Concerning the history of both chemical elements, according to Wikipedia, the free encyclopedia, calcium (from Latin

calx, genitive calcis, meaning “lime”) compounds were known as early as the first century, when the ancient Romans prepared lime as calcium oxide. However, calcium sulfate (also known as plaster of Paris or lime plaster) had been known much earlier: three statues were discovered in a buried pit at ‘Ain Ghazal in Jordan those were sculpted with lime plaster over armatures of reeds and twine. They were made in the pre-pottery Neolithic period, around 7200 BC. However, calcium in a pure state was not isolated until 1808, when the famous British chemist and inventor Sir Humphry Davy (1778–1829) electrolyzed a mixture of lime and mercuric oxide.^{3,4}

Phosphorus is a bit younger. The discovery of this chemical element in a pure state [its name given from Greek mythology, Φωσφόρος meaning “light-bearer” (Latin: Lucifer), referring to the “Morning Star,” the planet Venus] is credited to a German merchant and alchemist Hennig Brand (ca. 1630–1710) in 1669, although other alchemists might have discovered phosphorus around the same time. Brand experimented with urine, which contains considerable quantities of dissolved phosphates from normal metabolism. However, it was the famous French chemist Antoine Laurent Lavoisier (1743–1794), who recognized phosphorus as a chemical element in 1777. Interestingly, phosphorus appears to be the first element discovered since antiquity. To conclude these introductory exercises, the earliest research paper I have been able to find, containing the word “phosphorus” in the title belongs to the famous British natural philosopher, chemist, physicist and inventor Robert Boyle (1627–1691) and was published in 1693⁵ shortly after his death.

General Problems with Access to Old Publications

Due to large problems accessing the scientific literature published in the first half of the 19th century and even earlier, a deep investigation into the history of the subject still remains to be both fragmental and incomplete. That time, the scientific concepts were rather different from the modern ones and chemical formulae of the substances had not been introduced yet. Furthermore, scientific journals were rare and just a few of them are currently available in the electronic form. Luckily, a great many books published before the 20th century have been scanned by Google as a part of its project to make the world’s books discoverable online. This timely project by Google combined with the power of the modern electronic databases of scientific publications allows reconstructing the major historical milestones on calcium orthophosphates, which was often impossible for earlier review writers. For example, a paper of 1994 by

[†]As a mineral species, apatite was first recognized by the father of German geology Abraham Gottlob Werner (1750–1817) in 1786 and named by him from the ancient Greek ἀπατάω (apatao), “to mislead” or “to deceive,” because it had previously been mistaken for other minerals, such as beryl, tourmaline, chrysolite, amethyst, fluorite, etc. Currently, apatite is the name for a group of minerals with the same crystallographic structure and does not indicate one chemical composition. That is why the term “calcium apatite” is used in this review.

Table 1. Existing calcium orthophosphates and their major properties^{1,2}

Ca/P molar ratio	Compound	Formula	Solubility at 25°C, -log(K _s)	Solubility at 25°C, g/L	pH stability range in aqueous solutions at 25°C
0.5	Monocalcium phosphate monohydrate (MCPM)	Ca(H ₂ PO ₄) ₂ · H ₂ O	1.14	~18	0.0–2.0
0.5	Monocalcium phosphate anhydrous (MCPA or MCP)	Ca(H ₂ PO ₄) ₂	1.14	~17	c
1.0	Dicalcium phosphate dihydrate (DCPD), mineral brushite	CaHPO ₄ · 2H ₂ O	6.59	~0.088	2.0–6.0
1.0	Dicalcium phosphate anhydrous (DCPA or DCP), mineral monetite	CaHPO ₄	6.90	~0.048	c
1.33	Octacalcium phosphate (OCP)	Ca ₈ (HPO ₄) ₂ (PO ₄) ₄ · 5H ₂ O	96.6	~0.0081	5.5–7.0
1.5	α-Tricalcium phosphate (α-TCP)	α-Ca ₃ (PO ₄) ₂	25.5	~0.0025	a
1.5	β-Tricalcium phosphate (β-TCP)	β-Ca ₃ (PO ₄) ₂	28.9	~0.0005	a
1.2–2.2	Amorphous calcium phosphates (ACP)	Ca _x H _y (PO ₄) _z · nH ₂ O, n = 3 – 4.5; 15 – 20% H ₂ O	b	b	~5–12 ^d
1.5–1.67	Calcium-deficient hydroxyapatite (CDHA or Ca-def HA) ^e	Ca _{10-x} (HPO ₄) _x (PO ₄) _{6-x} (OH) _{2-x} (0 < x < 1)	~85	~0.0094	6.5–9.5
1.67	Hydroxyapatite (HA, HAp or OHAp)	Ca ₁₀ (PO ₄) ₆ (OH) ₂	116.8	~0.0003	9.5–12
1.67	Fluorapatite (FA or FAp)	Ca ₁₀ (PO ₄) ₆ F ₂	120.0	~0.0002	7–12
1.67	Oxyapatite (OA, OAp or OXA) ^f	Ca ₁₀ (PO ₄) ₆ O	~69	~0.087	a
2.0	Tetracalcium phosphate (TTCP or TetCP), mineral hilgenstockite	Ca ₄ (PO ₄) ₂ O	38–44	~0.0007	a

^aThese compounds cannot be precipitated from aqueous solutions. ^bCannot be measured precisely. However, the following values were found: 25.7 ± 0.1 (pH = 7.40), 29.9 ± 0.1 (pH = 6.00), 32.7 ± 0.1 (pH = 5.28). The comparative extent of dissolution in acidic buffer is: ACP > α-TCP > β-TCP > CDHA > HA > FA. ^cStable at temperatures above 100°C. ^dAlways metastable. ^eOccasionally, it is called “precipitated HA (PHA).” ^fExistence of OA remains questionable.

Driskell entitled: “Early history of calcium phosphate materials and coatings”⁶ starts from the classical publication of 1920 by Albee assisted by Morrison.⁷ In 1999, Shackelford published a paper: “Bioceramics—an historical perspective,”⁸ in which the same publication by Albee assisted by Morrison⁷ was mentioned as the earliest reference. The same is valid for the historical papers by Hulbert et al.^{9,10} and Shepperd.¹¹ Thus, it might create a false impression that calcium phosphates were unknown before 1920. Certainly, this is not the case; nevertheless, the precise sequence of the scientific events happened in the 18th century still remain poorly restorable, while the historical time scale of even earlier scientific events remain almost irrecoverable. This is mainly due to a lack of the citation practice existed in the scientific literature published in the 19th century and before. Besides, even nowadays, for the entire 18th century and approximately the first quarter of the 19th century, only scientific books digitalized by Google are widely available. No journal papers devoted to apatites and/or any type of calcium phosphates published before ~1820s have been found. However, in no case this means that they do not exist; presumably, they either have not been scanned yet (especially, this might be valid for discontinued scientific journals) or an access to the scanned versions is restricted to a limited amount of subscribers only.

Investigations and Knowledge on Calcium Orthophosphates

In the 18th century. According to the available literature, the history of calcium orthophosphates started in 1769. For example, in 1881 Roscoe and Schorlemmer¹² published the following statement: “Gahn, in 1769, discovered the existence of calcium phosphate in bones, but it was not until this fact was published by Scheele in 1771 that phosphorus was obtained from bone-ash, which has from that time invariably served for its preparation.”^{12,13} Simultaneously, the presence of phosphoric compounds was discovered in blood serum, which follows from a publication of 1770¹³ (please, note that the old-fashioned use of a long, medial or descending letter “s,” which is a form of the minuscule letter “s” formerly used where “s” occurred in the middle or at the beginning of a word has been changed to the modernized letter “s” for the reader’s understanding of the text): “The serum consists chemically of a coagulable matter, and water in which

¹²Johan Gottlieb Gahn (1745–1818) was a Swedish chemist and metallurgist, who discovered manganese in 1774.

¹³Carl Wilhelm Scheele (1742–1786) was a German-Swedish pharmaceutical chemist, who discovered oxygen (although Joseph Priestley published his findings first), as well as identified molybdenum, tungsten, barium and chlorine before Humphry Davy.

common sal ammoniac and phosphoric ammoniac, and generally common salt, and frequently selenites, and, fixed ammoniac, are dissolved.¹³ Furthermore, let me cite a publication of 1777:¹⁴ “I have only been informed of this discovery, by the *Gazette, Salulaire de Bouillon*, October, 1775. It is there said, that Mr Henry Gahn, a physician at Stockholm, has communicated a process for extracting from bones the saline matter in question; and that Mr Scheele had ascertained, that the earth of animals was composed of a calcareous substance united with the phosphoric acid. This discovery, continues the author of the article of the *Gazette*, belongs to Mr Gahn, and has been confirmed by later experiments.”¹⁴ Presumably, this citation might be considered as one of the earliest mentioning on calcium phosphates in the history.

Further, according to Shepperd,¹¹ the famous German chemist Martin Heinrich Klaproth (1743–1817) and the famous French chemist Joseph-Louis Proust (1754–1826) also studied calcium orthophosphates. Unfortunately, Shepperd has not provided any references to the publications by those great chemists. Nevertheless, a search performed among the Google books has provided some results. For example, in a French book published in 1790,¹⁵ one can find a subchapter entitled “Apatite. Phosphate de Chaux.” which is started from the following sentence: “C’est Mr Klaproth, qui à découvert le premier cette combinaison de la terre calcaire avec l’acide phosphorique.”¹⁵ Further, “Mr Proust dans une Lettre à Mr. d’Arcet a donné l’Analyse de cette pierre, qui est une combinaison de la terre calcaire avec l’acide phosphorique.”¹⁵ One can see that, by that time, apatite was already recognized as a calcium phosphate, which is also confirmed by a German book published in 1789,¹⁶ in which “Apatit” was called “die Phosphorsäure mit Kalkerde.”¹⁶

Furthermore, according to a book written by Lavoisier,¹⁷ the production process of orthophosphoric acid by decomposition of calcined bones in sulfuric acid has been known since, at least, 1790: “The bones of adult animals being calcined to whiteness, are pounded, and passed through a fine silk sieve; pour upon the fine powder a quantity of dilute sulphuric acid, less than is sufficient for dissolving the whole. This acid unites with the calcareous earth of the bones into a sulphat of lime, and the phosphoric acid remains free in the liquor.”¹⁷ Further, the production process of white phosphorus has been described: “The liquid is decanted off, and the residuum washed with boiling water; this water which has been used to wash out the adhering acid is joined with what was before decanted off, and the whole is gradually evaporated; the dissolved sulphat of lime cristallizes in form of silky threads, which are removed, and by continuing the evaporation we procure the phosphoric acid under the appearance of a white pellucid glass. When this is powdered, and mixed with one third its weight of charcoal, we procure very pure phosphorus by sublimation.”¹⁷

In the last decade of the 18th century, further investigations on calcium orthophosphates were performed by two famous French chemists Antoine François, comte de Fourcroy (1755–1809) and Nicolas Louis Vauquelin (1763–1829), who discovered an existence of acidic calcium orthophosphates, currently known as MCPM, MCPA, DCPD and DCPA (Table 1). For example,

according to a book, published in 1816,¹⁸ “Super-Phosphate of Lime was discovered in 1795, by Fourcroy and Vauquelin. It had indeed been often formed before, but chemists had neglected to examine it.”¹⁸ In addition, let me cite a book by Fourcroy, 1804:¹⁹ “A few years ago this salt, which I here denominate the acid phosphate of lime, was unknown. Scheele very properly remarked that the saline earth of bones was dissolved by an acid in human urine, but he did not observe that this union between phosphoric acid and the bony phosphate, makes a kind of permanent and particular salt different from the latter. It was in the year 1795, the third year of the Republic, that I discovered it, with Citizen Vauquelin, in a connected series of experiments upon bony matters; wherein we proved that the calcareous phosphate which constitutes the solid base, is only in part decomposable by acids, and that the portion of phosphoric acid which is separated, retains in solution phosphate of lime, which it then defends from all subsequent alteration by other acids.”¹⁹ Furthermore, in his book Fourcroy mentioned other contributors to early studies on calcium orthophosphates: “Citizens Nicholas of Nancy, Pelletrier, Berniard, Bullion, in France; Westrumb, and several chemists in Germany; Bonviosin, at Turin; Tenant, Pearson, and some others in England, multiplied their inquiries and experiments.”¹⁹ Thus, one can notice that in the end of the 18th century, the subject of calcium orthophosphates was extensively investigated by a number of researchers in several countries of the Western Europe.

To conclude this section, one should notice that the basic knowledge on calcium orthophosphates became available by the end of the 18th century.

In the 19th century. For the 19th century, both scientific books and a small amount of scientific journals are available; however, for the first half of the 19th century, journals are almost unavailable. Nevertheless, according to the available literature, a real explosion of the scientific knowledge on calcium orthophosphates occurred in the 19th century. Namely, Fourcroy¹⁹ stated that presence of water in acidic calcium orthophosphates was known by 1804: “The acid phosphate of lime contains a remarkable quantity of water: the crystallization immediately softens and becomes liquefied by the fire.”¹⁹ Unfortunately, based on this citation, it is impossible to differentiate which type of an acidic calcium orthophosphate MCPM or DCPD Fourcroy born in mind. Knowledge on acidic calcium orthophosphates was further developed in 1805:²⁰ “Acid Phosphate of Lime is formed either by taking away a part of the base by sulphuric, nitric, or muriatic acid, or by superadding phosphoric acid to the last described phosphate,”²⁰ and in 1806:²¹ “In this way were distinguished among the salts two combinations, one neutral, and one with an excess of acid; and these were supposed to be determinate, as in sulphate and super-sulphate of potassa, or the phosphate and super-phosphate of lime.”²¹ More precise information on acidic calcium orthophosphates became available by 1819:²² “Biphosphate of Lime. This salt may be formed by digesting phosphate of lime in phosphoric acid, dissolved in hot water.”²² “Quadriphosphate of Lime.—Glassy Phosphoric Acid of the Apothecaries. This salt may be formed by digesting, for some time, finely powdered phosphate of lime in a quantity of sulphuric acid, sufficient to saturate all the lime of the phosphate,

and afterwards diluting the mixture with a sufficient quantity of water, and filtering. Sulphate of lime remains on the filter, and a liquid quadriphosphate passes through."²² Presumably, aqueous solutions of DCPD and MCPM, respectively, were prepared; therefore, we can claim that MCPM and DCPD were differentiated by 1819. Furthermore: "Subphosphate of Lime.—This salt occurs native under the names of apatite or asparagus stone."²² Thus, the differences between HA (subphosphate of lime) and TCP (phosphate of lime) were established by 1819.

The preparation process of a pure calcium orthophosphate currently known as CDHA was developed by 1813:²³ "Phosphat of lime, proper. As this salt constitutes the basis of bones, it is not necessary to prepare it artificially. It may be obtained in a state of purity by the following process: Calcine the bones to whiteness, reduce them to powder, and wash them repeatedly with water, to separate several soluble salts which are present. Dissolve the whole in muriatic acid, and precipitate by means of ammonia. The precipitate, when well washed and dried, is pure phosphat of lime." One can see that the basics of this process are still used to produce chemically pure calcium orthophosphates from the natural resources (phosphate ore and bones). In 1819, the major properties were described as follows:²² "Phosphate of lime is a white insoluble powder, destitute of taste, and unaltered by exposure to air. It is soluble in hydrochloric (muriatic) and nitric acids, and may be precipitated from solution in them by means of ammonia. When exposed to a very violent heat, it undergoes a kind of fusion, and is converted into a white semi-transparent porcelain."²² However, that knowledge on the thermal properties of phosphate of lime was based on the Fourcroy's investigations:¹⁹ "The phosphate of lime is extremely difficult to fuse; nevertheless, by strong fire, such as that of a glass-house, it softens and acquires a semi-transparence like the grain of porcelain."¹⁹ Thus, calcium phosphate ceramics has been known, since, at least, 1804.

In the 4th edition of Encyclopædia Britannica (1810), applications of calcium orthophosphates were described as follows:²⁴ "The phosphate of lime is of great importance in chemistry, for the purpose of extracting phosphoric acid, to be decomposed to obtain phosphorus. It is also employed for making cupels, for polishing metals and precious stones, and for removing spots of greasy from linen, paper, and silk. It is used in medicine as a remedy for rickets, to correct the supposed effects of acids in softening the bones."²⁴ Although it is slightly beyond the subject, one should mention, that calcium phosphite [$\text{Ca}_3(\text{PO}_3)_2$] is also mentioned in that edition of Encyclopædia Britannica, as "phosphite of lime."²⁴ A chemical term "tribasic phosphate of lime," which fully corresponds to α -TCP and β -TCP, has been known since, at least, 1832.²⁵

Concerning publications in scientific journals, in the first half of the 19th century, research papers on calcium apatites and other calcium orthophosphates were published by the famous Swedish chemist Jöns Jacob Berzelius (1779–1848),^{26,27} as well as by M. Baruel²⁸ and J.D. Smith.²⁹ For example, in a book by Bache, published in 1819,²² the following statement on the Berzelius's contribution was published: "According to an analysis by Berzelius, calculated in numbers, in which the equivalent number for lime is assumed, phosphate of lime is composed of Phosphoric acid 34.3;

Lime 29.0, one atom; so that it appears that the composition of this salt cannot be reconciled with the atomic theory."²² However, as early as 1804, Fourcroy¹⁹ wrote: "100 parts of phosphate of lime contain, according to the analysis of Citizens Fourcroy and Vauquelin, Phosphoric acid 41 Lime 59,"¹⁹ while the chemical composition of acid phosphate of lime he described as follows: "An accurate analysis of this salt affords the following proportions of component parts, Lime 45 Phosphoric acid 54."¹⁹

A little bit later, the famous German chemist Eilhard Mitscherlich (1794–1863), who was a learner and a friend of J.J. Berzelius and who is, perhaps, best remembered today for his law of isomorphism (1819), also worked in this area. For example, the earliest chemical formulae of calcium phosphates were published in 1844 on page 69 of Mitscherlich's book³⁰ as $2.\text{Ca}^2\text{P}$ and $5.\text{Ca}^2\text{P}$. Besides, in 1849, it was written that "M. J. L. Lassaigne, at the meeting of the Academy of Sciences of Paris, of the 15th January, presented a memoir upon this subject, showing by experiments that the phosphate and carbonate of lime are introduced into plants in solution in water containing carbonic acid, which had before been shown as to the phosphate by M. Dumas, and has long been known as to the carbonate."³¹ Thus, a higher solubility of both calcium orthophosphates and calcium carbonate in weak acids was already known in 1849.

The second half of the 19th century started with *Chemistry* by Wilson, published in 1850.³² The following parts from that book are worth citing. "797. Phosphates of Lime.—There are many compounds of lime and phosphoric acid, owing to the peculiarity of that acid in relation to the number of equivalents of base it combines with at once. The most interesting phosphate of lime is that which occurs in bones, and is distinguished as the bone-earth phosphate, $3\text{CaO},\text{PO}_5$,"³² Thus, various types of calcium orthophosphates were known by 1850. However, the preparation technique sounds unusual to the modern readers: "The phosphorus combines in part with the oxygen of the lime, CaO , to form phosphoric acid, and this with undecomposed lime, to form phosphate of lime, CaO,PO_5 . At the same time another portion of the phosphorus combines with the calcium of the lime, forming phosphuret of calcium, CaP ."¹⁶⁴ In *Chemistry* by Brande and Taylor, published in 1863,³³ one can find the following statements: "Common Phosphate of Lime; Tribasic Phosphate of Lime; Bone Phosphate; [$3(\text{CaO}),\text{PO}_5$]. This salt occurs abundantly in bone-ash, and is found as a mineral product."³³ Furthermore, "Native phosphate of lime (bone phosphate) occurs in apatite, moroxite, phosphorite, and asparagus stone; its primitive form is a six-sided prism: it also occurs in some volcanic products."³³ Thus, a similarity between the inorganic phase of bones and calcium orthophosphate rocks of natural origin (apatite and phosphorites) was known by 1863. "When a solution of bone-earth in hydrochloric or nitric acid is boiled to expel all carbonic acid, and decomposed by caustic ammonia, the bone-phosphate separates in the form of a bulky precipitate, which, when perfectly dried, is white and amorphous."³³ This statement is really astonishing because it might be considered as the first mention on ACP,³⁴ 32 years before discovering X-rays in 1895 by the famous German scientist Wilhelm Conrad Röntgen (1845–1923)! Next citation: "The substance known under the name of coprolites, and which appear

to be the excrements of fossil reptiles, also abound in phosphate of lime³³ means that by 1863 researchers were aware on this fact.

Further historical description is based on journal publications only. C. Morfit,³⁵ Robert Warington [there were two chemists with this name, presumably, a father (1807–1867) and a son (1838–1907)], who performed the earliest well documented systematic studies of the outstanding quality,³⁶⁻³⁹ and R. Fresenius⁴⁰ also worked with calcium orthophosphates. Furthermore, let me cite a paragraph from reference 37: “Mitscherlich tells us, that when chloride of calcium is added to ordinary disodic phosphate, the latter being maintained in excess, the precipitate formed is tricalcic phosphate, while the solution becomes acid from the production of monosodic phosphate. Berzelius, on the contrary, states, that the precipitate formed under these conditions is not tricalcic phosphate, but the octocalcic triphosphate, which lie has elsewhere described. All experimenters agree, that when the operation is reversed, and disodic phosphate is poured into an excess of chloride of calcium, the precipitate is neither tricalcic nor octocalcic, but dicalcic phosphate.”³⁷ Thus, TCP, DCP and OCP have been known since, at least, 1866, while, in fact, a bit earlier. Furthermore, the researchers were already aware on the fact that the type of a precipitated calcium orthophosphate depended on a sequence of the mixing reagents.

Among the available publications written by two Robert Waringtons,³⁶⁻³⁹ reference 37 by Robert Warington Jr. deserves both special attention and extensive citations. For example, to prove that OCP indeed was already known in 1866, let me make another citation from reference 37: “Octocalcic phosphate can only be produced by the simultaneous formation of monosodic phosphate: $8\text{CaCl}_2 + 5\text{Na}_4\text{H}_2\text{P}_2\text{O}_8 = \text{Ca}_8\text{H}_2\text{P}_6\text{O}_{24} + 16\text{NaCl} + 2\text{Na}_2\text{H}_4\text{P}_2\text{O}_8$.”³⁷

One can see a balanced chemical equation, fully identical to the modern ones. It is hard to believe that it was published in 1866! It is interesting to note that only 22 years appeared to be enough to perform a transition from the earliest primitive chemical formulae without oxygen, such as $2\text{Ca}^2\text{P}$ and $5\text{Ca}^2\text{P}$,³⁰ to the modern chemical equations. More to the point, the chemical formulae of hydrated forms of calcium orthophosphates were known by 1866: “8.73 grs. of the vacuum-dried salt, lost on ignition 12.30 grains, or 26.35 per cent.; the formula $\text{Ca}_2\text{H}_2\text{P}_2\text{O}_8 \cdot 4\text{H}_2\text{O}$, demands 26.16 per cent. of water.”³⁷ Needless to explain, that “ $\text{Ca}_2\text{H}_2\text{P}_2\text{O}_8 \cdot 4\text{H}_2\text{O}$ ” represents two molecules of DCPD (see Table 1). Furthermore, “It is interesting to observe that while disodic phosphate is of an alkaline nature, dicalcic phosphate possesses faint acid properties.”³⁷ More to the point, the form and shape of DCPD crystals were described as well: “The crystalline form of the dicalcic tetrahydrated phosphate has been examined by Professor Church. He describes the crystals as thin rhomboïdal plates, of which the diagonally opposite acute angles are sometimes truncated, hexagonal forms being thus produced. This truncation seems to be occasionally hemihedral, and then may proceed up to the diagonal between obtuse angles; from this change triangular forms arise. Other modifications are also met with.”³⁷ Another interesting conclusion might be found here: “We may then safely affirm that whenever dicalcic phosphate, octocalcic triphosphate, or any phosphate of intermediate composition,

is precipitated from solution by ammonia, the salt obtained will be the octocalcic triphosphate; a tricalcic phosphate cannot be obtained in this manner. The following is probably a type of the reaction: $4\text{Ca}_2\text{H}_2\text{P}_2\text{O}_8 + 6\text{NH}_3 = \text{Ca}_8\text{H}_2\text{P}_6\text{O}_{24} + 6\text{NH}_4 \cdot \text{P}_2\text{O}_8$.”³⁷

This seems to be the earliest mentioning on the fact that TCP cannot be precipitated from the aqueous solutions (currently we know that ACP or CDHA are precipitated instead). In addition, the following citation from the same publication: “It is quite possible that precipitated tricalcic phosphate may possess somewhat different solubilities, when prepared by different methods; this difference can, however, scarcely be great”³⁷ has two important consequences: (1) by 1866 this fact was not quite clear yet and (2) it indirectly points to variability in the Ca/P ratio for the precipitated ACP or CDHA, which is the major reason of different solubilities.

The latest available publication by Warington³⁹ was devoted to the hydrolysis of a freshly precipitated TCP (i.e., either ACP or CDHA) to the stoichiometric HA under continuous (up to 50 h) boiling in distilled water. From the results of numerous chemical analyses the author concluded that during boiling an aqueous suspension of the TCP was slowly transformed to a suspension of $3\text{Ca}_3\text{P}_2\text{O}_8 \cdot \text{CaOH}_2\text{O}$ (i.e., HA, see Table 1) and soluble acidic calcium orthophosphates. The following conclusion was made: “Since it appears that all phosphates of calcium less basic than apatite are unstable under the continued action of pure water, it seems probable that a more exact examination of natural phosphates would show that many phosphates now regarded as tricalcic are in fact of a more basic nature.”³⁹ Thus, the apatitic nature of the majority of natural calcium orthophosphates has been predicted in 1873. The next available journal article on the TCP hydrolysis was published in 1929 only.⁴¹

The first accessible journal paper on detection and preservation techniques of various deposits, including calcium orthophosphates, was published in 1852.⁴² Presence of calcium orthophosphates in teakwood was established in 1862.⁴³ Various analytical topics on calcium orthophosphate chemistry has been studied since at least 1863⁴⁴ and remained to be a subject of active research until approximately the 1910s.⁴⁵⁻⁵⁴

A popular fertilizer superphosphate, which represents “a mixture of the last-mentioned compound and sulphate of lime”⁵⁵ has been known since, at least, 1803: “The phosphoric acid separated from that portion of lime, immediately combines with the rest of the phosphate of lime, and forms super phosphate of lime, which is not farther decomposable by sulphuric acid.”⁵⁶ More than 20 research papers on superphosphate were published by the beginning of the 20th century, which indicated to the importance of this chemical for the human being. To give the appropriate tribute to those early investigators and restore the historical perspective, it is worth citing them all.⁵⁷⁻⁷⁹ One can see that almost all of these studies were performed and published by single researchers (see individual comments to refs. 58 and 65), while the majority of the investigations were devoted to analytical chemistry.

More to the point, let me make a citation from a publication by Wells of 1906:⁸⁰ “The apparent constancy of the proportion of carbonate and phosphate of calcium in bones made

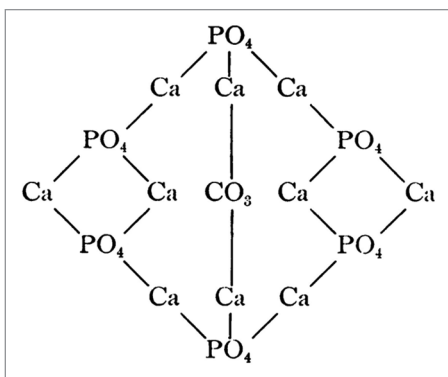


Figure 1. The first available structure of a bone mineral, currently known as carbonateapatite. Reprinted from reference 80.

an impression on Hoppe-Seyler in 1862, and we find him speculating on the possibility of the components of the two salts being joined together to form one giant molecule: $3 [Ca_3 (PO_4)_2] - CaCO_3$, which he imagined might be united in some such way,⁸⁰ see **Figure 1**. Further, Wells mentioned: “This formula is interesting chiefly from the historical standpoint, but it serves to emphasize the tendency of these salts to appear in nearly constant proportions in the animal body, a fact possibly of some importance.”⁸⁰ Obviously, the atomic arrangement shown in **Figure 1** represents the earliest structural drawing of a single molecule of a calcium orthophosphate currently known as carbonateapatite. An attentive reader will notice two different types of calcium [currently known as Ca(1) and Ca(2)] in that structure.

Although vitrification properties of some forms of calcium orthophosphates at heating have been known since, at least, 1804,¹⁹ the first accessible journal paper on this topic was published in 1877.⁸¹ The modern chemical formula of perfectly transparent crystals of natural FA as $Ca_5(PO_4)_3F$ has been known since, at least, 1873,⁸² while the major crystallographic faces of a natural calcium apatite were described in 1883.⁸³ Chemical formulae of DCP (as “Mono-Hydrogen Calcium Orthophosphate, $H_2Ca(PO_4)_2$ ”) and MCP [as “Tetra-Hydrogen Calcium Phosphate, $H_4Ca(PO_4)_2$ ”) have been known since, at least, 1879.⁵⁵ Interestingly that in a publication of 1871, the chemical formulae of calcium orthophosphates were written in different ways: $3CaO PO_5$ for apatite and $CaO 2HO PO_5$ for “some acid phosphate of lime.”⁵⁹

Neutral phosphates of lime were further investigated in 1872.⁸⁴ Besides, in the 19th century, calcium apatites were considered as combined compounds, which results from this citation: “Calcium phosphate, combined with calcium chloride or calcium fluoride, occurs in the well-known minerals, apatite and osteolite.”⁵⁵ One might guess that, in the 19th century, the atomic arrangement of single molecule of carbonateapatite (**Fig. 1**) could inspire researchers to compose similar drawings for the single molecules of FA, HA and/or chlorapatite; however, I have not succeeded to find anything on this matter.

Chemical equations, describing various interactions between calcium phosphates and other chemicals have been known since at least 1863. For example, the afore-cited production processes

of both orthophosphoric acid and white phosphorus from the Lavoisier book,¹⁷ in 1863 were written using chemical equations:³³ “When bone-phosphate is digested in dilute sulphuric acid, it is resolved into sulphate of lime and (if a sufficiency of sulphuric acid be used) phosphoric acid: $3(CaO), PO_5 + 3SO_3 = 3(CaO, SO_3) + PO_5$.”³³ Furthermore, various types of phosphates (namely, metaphosphate, acid phosphate) and differences in their solubility were known by 1881:¹² “In order to prepare phosphorus, the bone-ash is first mixed with so much dilute sulphuric acid as to form the acid phosphate: $Ca_3 (PO_4)_2 + 2H_2SO_4 = CaH_4 (PO_4)_2 + 2CaSO_4$.

The solution of this soluble acid phosphate is next poured off from the precipitated gypsum, and evaporated to dryness, after which, the solid residue being heated to redness, water is given off and calcium metaphosphate formed: $CaH_4 (PO_4)_2 = Ca (PO_3)_2 + 2H_2O$.

This salt is then carefully mixed with charcoal, and heated to bright redness in earthenware retorts shown in **Figure 147**, when the following change takes place: $Ca (PO_3)_2 + 10C = P_4 + Ca_3 (PO_4)_2 + 10CO$.¹²

The quantitative analysis of a calcium orthophosphate was performed in 1884,⁸⁵ followed by remarks by C. Glaser in 1885.⁸⁶ In the 1880s, occurrence of a calcium apatite⁸⁷ and TTCP⁸⁸⁻⁹⁰ in metallurgical slags was discovered. An attempt of a direct estimation of phosphoric acid as the tribasic phosphate of lime was performed in 1888.⁹¹ A chemical interaction of TCP with carbon dioxide and iron hydroxide was investigated in 1891.⁹²

To conclude this section, one should notice, that the major discoveries in chemistry of calcium orthophosphates were made in the 19th century.

From 1900 until 1940. As the modern scientific databases comprise scientific papers published since 1900, the history of calcium orthophosphates in the 20th century is based on journal publications only. This approach allows establishing the real chronological order.

The 20th century started with the systematic studies performed by F.K. Cameron with coworkers^{79,93-99} and H. Bassett.¹⁰⁰⁻¹⁰³ Namely, in 1908, Bassett composed the first version of the solubility diagram $CaO-P_2O_5-H_2O$.¹⁰² According to the literature,^{12,55,104} by that time researchers already operated with individual calcium orthophosphates. Binary salts of calcium orthophosphates with orthophosphates of other chemical elements have been known since at least 1911.¹⁰⁵ Currently well-known chemical route of CDHA preparation by mixing of aqueous solutions of calcium nitrate and K_2HPO_4 [now $(NH_4)_2HPO_4$ is used instead] was investigated conductometrically in 1915,¹⁰⁶ while a neutralization reaction of H_3PO_4 by $Ca(OH)_2$ was investigated in 1923.¹⁰⁷ The first paper on in vitro mineralization using aqueous solutions containing ions of calcium and orthophosphate was published in 1926,¹⁰⁸ followed by a publication of 1933.¹⁰⁹ The latter studies might be considered as predecessors of current mineralization investigations using simulating body fluid (SBF) and other artificial simulating solutions.

The crystal structure of FA was established in 1931,¹¹⁰ followed by a great study on the structural characteristics of apatite-like calcium orthophosphates of various origin in 1933.¹¹¹ Such

terms as hydroxyfluorapatite, $\text{Ca}_{10}(\text{F},\text{OH})_2(\text{PO}_4)_6$, OA and carbonateapatite were already known. Besides, currently unknown substance “a hydrate of tricalcium phosphate, $\text{Ca}_3(\text{H}_2\text{O})_2(\text{PO}_4)_6$ ” with the molecular weight of 966.4 and apatite-like diffraction pattern (obviously, it was CDHA with $x = 1$, see Table 1) was mentioned as well.¹¹¹ Furthermore, the solubility data of several calcium orthophosphates were updated in 1931.^{112,113} Additionally, in 1931–1933, Bredig et al.,¹¹⁴ Trömel¹¹⁵ and Schneiderhöhn (a reference was not found) differentiated α - and β -modifications of TCP (see Table 1) and created the initial versions of the high-temperature diagram for the binary system $\text{CaO}-\text{P}_2\text{O}_5$. Very popular at the turn of this millennium silicon- (or silica-) contained calcium orthophosphates, in fact, appear to be known since, at least, 1937,^{116,117} simultaneously with defluorination studies of natural phosphate rocks,¹¹⁷⁻¹¹⁹ while the earliest research paper on an application of calcium orthophosphates in chromatography was published in 1942.¹²⁰

In 1940, the available level of knowledge on basic calcium orthophosphates (TCP, TTCP and apatites) was summarized into a big review,¹²¹ which might be considered as the first comprehensive review on the subject. Interestingly, but the authors of that review have written about HA that “Existence as a unique stoichiometric compound doubtful,”¹²¹ which is a clear indication to the great difficulties to synthesize HA but not CDHA. That time, the existence of OA was uncertain.¹²¹ Besides, in 1940, a fundamental study on the equilibrium in the system $\text{CaO}-\text{P}_2\text{O}_5-\text{H}_2\text{O}$ was published.¹²²

To finalize this chemical section, one should mention that by 1928 it was clearly known that TCP could not be prepared by wet-precipitation. Let me cite: “We have been unable to find any evidence of the existence of a molecular species with the formula $\text{Ca}_3(\text{PO}_4)_2$. Precipitates of this ‘substance’ rarely have the correct empirical composition and they cannot be purified by recrystallization. The evidence is such as to lead us to suspect that there may be no such chemical entity as $\text{Ca}_3(\text{PO}_4)_2$. No one has succeeded in preparing it by precipitation, bearing out the theoretical objections to such a reaction on the grounds that fifth order reactions do not occur. We do not take the position that there can be no compound with this formula. It may be found possible to synthesize it by other methods, but so far no one has succeeded in preparing it by precipitation.”¹²³ Similar conclusions were made by other researchers.¹²⁴ Nevertheless, this knowledge was not common yet, since, in 1935, a report was published that “Tricalcium phosphate monohydrate was prepared by the slow addition of calcium chloride solution to a constantly agitated alkaline solution of disodium phosphate, maintained at 65° to 70°C .”¹²⁵ This controversy has been explained in reference 121 by a matter of definitions: “The terms ‘tricalcium phosphate’ and ‘hydroxyapatite’ are very widely and very loosely used. For example, some authors use the former for any precipitate more basic than dicalcium phosphate, although such precipitates have been frequently shown to have an apatite lattice or to be mixtures of dicalcium phosphate and an apatite. Others confine the use of the term to those precipitates with $\text{P}_2\text{O}_5:\text{CaO}$ ratios approaching that of $\text{Ca}_3(\text{PO}_4)_2$.”¹²¹

More recent (after 1940) publications on chemistry of calcium orthophosphates are not considered, since they are well known.

Early Publications on Calcium Orthophosphates of Geological Origin

As written above, apatite was recognized as a calcium phosphate by 1789.^{15,16} As early as 1794, Kirwan¹²⁶ wrote a section “Phosphorite. Apatite of Werner,”¹²⁶ in which one can read the following: “In Spain, it is found in extensive strata forming entire mountains; ... Sometimes also crystallized in Germany, and of greenish colour. In Saxony, it is found in low hexahedral prisms with truncated edges and angles, the planes of the sides longitudinally seamed, or in hexangular tables heaped one on the other.” Thus, calcium orthophosphates of geological origin has been known since the end of the 18th century. At the very beginning of the 19th century (in 1805), Nisbet²⁰ wrote: “Phosphated Lime, apatite or phosphorite, has been found in an amorphous state in Hungary, and forming entire mountains in Spain. It is also found in truncated hexahedral, longitudinally striated prisms, laminated in their transverse fracture, and generally with tin and fluor. Klaproth found it to contain acid 45, lime 55.”²⁰

In 1809, Murray¹²⁷ wrote on natural phosphorite: “Its colour is yellowish or greyish white, without lustre or transparency; rough to the touch; and having a specific gravity of 2.8. This substance was analysed by Pellerier, who found it to consist of lime 59, phosphoric acid 34, fluoric acid 2.5, silice 2, iron 1, with a trace of carbonic and muriatic acids.”¹²⁷ Thus, a complex quantitative composition of natural phosphorites was established by 1809. Eleven years afterwards (in 1820), R. Jameson in his fundamental book: “A system of mineralogy”¹²⁸ published a section entitled “Genus II. APATITE,”¹²⁸ in which the major information on physical, chemical, crystallographic properties of natural apatites and phosphorites, as well as the geographic locations of major deposits were summarized. Shortly afterwards (in 1822), D. Lowry published a catechism book “Conversations on mineralogy,”¹²⁹ from which a self-explanatory “discussion” is worth citing:

“The family of phosphates of lime contains but two species, apatite and phosphorite.

Frances: Are they very different from each other?

Mrs. L.: In appearance they are, but not in composition; apatite is generally crystallized, and strongly translucent, or transparent; but phosphorite is always amorphous and opaque.”¹²⁹ Thus, the key similarities and differences between two major types of calcium orthophosphates of geological origin were established by 1822.

Concerning journal papers on the subject, the earliest publication on calcium orthophosphates of geological origin I have managed to find was published in 1873,⁸² followed by another one dedicated to deposits of natural calcium orthophosphates was published in 1889.¹³⁰ Presumably, the latter publication might be considered as the first review paper on calcium orthophosphates, in which the author described various types of natural phosphate deposits, their formation, as well as possible utilization, mainly as fertilizers. Next available scientific publications on natural calcium orthophosphates were published in 1895,¹³¹ 1901,^{132,133} 1902¹³⁴⁻¹³⁶ and 1904.¹³⁷ An important study on the presence of

orthophosphates of various chemical elements, including calcium, in soil was published in 1906;¹³⁸ however, this subject is beyond the scope of this review.

Studies on the Presence of Calcium Orthophosphates in Living Organisms

Studies performed in the 18th century. As mentioned above, the presence of calcium orthophosphates in bones has been known since the 1770s.^{12,13} Although the presence of phosphorus in urine was established in 1669 by Brand, knowledge on dissolved calcium in urine is available since at least the 1780s:¹³⁹ “We have seen that urine contains many peculiar salts; these salts are combinations of the phosphoric acid with volatile alkali, soda, and lime, and the base of the calculus of the bladder.”¹³⁹ According to another publication,¹⁴⁰ the discovery of calcium orthophosphates in urine is related to the great chemists Scheele and Lavoisier: “The immortal, and ever to be deplored, Lavoisier supposed these substances to consist of acidulous phosphate of lime and animal matter, many of them being partially fusible; but still it was the unrivalled Scheele who discovered that the urine of healthy persons contains superphosphate, or acidulous phosphate, of lime; and who also indicated the experiment which verified his opinion, that phosphate of lime is the basis of bone.”¹⁴⁰

A special chapter entitled “Concerning the bones of animals”¹³⁹ was published in 1788 as a part of the de Fourcroy’s book.¹³⁹ Several records from that chapter are worth citing: “These hard substances cannot be considered as passive in the animal economy, they are true secretory organs, which separate from the blood and other humours a peculiar saline substance, of which they are the reservoir, or place of deposition.”¹³⁹ This is the correct description of the role of bones in general metabolism. “The bones of men and of quadrupeds, which alone have been hitherto examined by chemists, are not earthy matters, as was formerly supposed: they contain a certain quantity of gelatinous matter, dispersed in small cavities, formed by the interval between the solid parts which compose their texture; and the solid parts themselves, though they seem to resemble earthy substances by their insolubility and firmness, have been for several years past acknowledged to be a true neutral salt, consisting of phosphoric acid and lime.”¹³⁹ Thus, the bioorganic/inorganic composite nature of bones has been known since, at least, 1788.

Concerning the level of knowledge on the presence of calcium orthophosphates in teeth and other calcified tissues of animals, available by the end of the 18th century, let me cite three self-explanatory sentences from a publication of 1797:¹⁴¹ “More recently, Berniard (Journal de Physique, Octobre, 1781) obtained phosphoric acid not only from fossil bones, from those of the whale and sea-horse, but from the tooth of the manati and the grinder of the elephant. It has also been extracted from ivory. In short, they who have experimentally attended to this subject have agreed, that animal bones are chiefly composed of phosphoric acid and calcareous earth, or are the phosphate of lime: and that their teeth consist in the main, of the like materials.”¹⁴¹

Studies performed in the 19th century. Further investigations on calcium orthophosphates in living organisms were performed in the 19th century. For example, the structure, composition, properties and formation mechanisms of bones were described in details in the London medical dictionary, published in 1809.¹⁴² The following statements from that dictionary are worth citing: “Bones consist of fibers crossing each other in different directions,”¹⁴² “The substance of bones is now known to be a calcareous phosphat, which is deposited by exhalent arteries; and this substance is constantly renovated, while an equal portion is carried off by absorption,” “Bones, we have said, owe their solidity to phosphorated lime. The bones of an adult contain the greatest proportion of earth; those of a foetus, of gelatin. Fish bones, from Mr. Accum’s experiments contain one-sixth part more of phosphoric acid than the bones of quadrupeds. Carbonated alkalis decompose the phosphat of lime in bones. They contain also a small proportion of selenite, carbonate of lime, and, according to Proust, of mineral alkali.”¹⁴² Thus, the presence of carbonates and other trace elements in the mineral phase of bones has been known since, at least, 1809. Similar is valid for the self-renovating properties of bones. The following self-explanatory citation from a book published in 1812¹⁴³ is worth mentioning: “It is remarkable, that though phosphate of lime is always found in the urine of adults, this salt is not evacuated by infants. The rapid formation of the bones, in the first periods of life, requires that there should be no waste of any of the phosphoric salts; and Nature, ever provident, has provided accordingly.”¹⁴³

Furthermore, according to the Fourcroy’s book, published in 1804,¹⁹ the presence of calcium orthophosphates in milk and blood was already known: “Citizens Berthollet and Fourcroy confirmed the discovery of Scheele respecting the presence of phosphate of lime in human urine. They found it also in milk, in blood, in the muscles, in jelly, etc.”¹⁹ Besides, as seen from a catechism book by Sir Humphry Davy, published in 1814,¹⁴⁴ the general principles of bone and teeth formation (biomineralization) were already known: “During the earliest period of animal life they consist almost entirely of a gelatinous membrane of the form of the bones, but of a loose spongy texture, the cells or cavities of which are destined to be filled with phosphat of lime; it is the gradual acquisition of this salt which gives to the bones their subsequent hardness and durability. Infants first receive it from their mother’s milk, and afterwards derive it from all animal and from most vegetable food, especially farinaceous substances, such as wheat flour, which contain it in sensible quantities. A portion of the phosphat after the bones of the infant have been sufficiently expanded and solidified, is deposited in the teeth, which consist at first of only a gelatinous membrane or case, fitted for the reception of this salt; and which, after acquiring hardness within the gum, gradually protrude from it.”¹⁴⁴ What is more, such disease as rickets (rachitis) was already known to be caused by deficiency of calcium phosphates: “Pray, Mrs. B. does not the disease of the bones of children, called the rickets, proceed from a deficiency of phosphat of lime?” and response: “The other cause of this disorder is an imperfect digestion and assimilation of the food, attended with an excess of acid, which

counteracts the formation of phosphat of lime.¹⁴⁴ Furthermore, according to the available literature,¹⁴⁵ one can conclude, that the correct basic knowledge on the structure, chemical composition and properties of bones was obtained by 1820.

The earliest journal publication, I have been able to find, devoted to the importance of calcium orthophosphates to bone health was published in 1842,¹⁴⁶ followed by a study published in 1895,¹⁴⁷ while those on calcium phosphates of bones were published by Aeby in 1872¹⁴⁸ and 1873,^{149,150} followed by papers written by other researchers.^{151,152}

In spite of the aforementioned achievements, basic research on bones kept going. Namely, compositional differences between bones belong to young and old individuals were extensively investigated in the middle of the 19th century. For example, let me cite a summary on this topic, published in 1928:¹⁵³ “In 1855 Frémy concluded that in humans there is, with increasing age, a relative increase of CaCO_3 with respect to calcium phosphate. Von Recklinghausen in 1858 concluded from his own analyses and from the work of Bibra (1844), of Stark (1845), of Heintz (1849), and of Frémy, that there was no observable difference in composition between the bones of young and those of old individuals. In 1860 Milne Edwards reported that his own analyses agreed with those of Bibra and of Frémy in showing that the proportion of carbonate in the bones of young animals was smaller than in adult bone. Zalesky in 1866 reviewed the literature and concluded that the bones of children of various ages have the same composition as those of adults, not only as a whole, but also as regards the proportion of individual constituents. He pointed out that the methods of determining CO_2 employed by previous investigators were defective. In 1872 Wildt analyzed the ashed bones of rabbits of different ages and found an increase in the proportion of CO_2 with increasing age. Weiske in 1889 analyzed the ashed bones of birds and found an increase in CaO and CO_2 with advancing age, while the P_2O_5 remained constant. Graffenberger in 1891 analyzed the ashed bones of rabbits and also found an increase of the ratio calcium carbonate: calcium phosphate with increasing age.”¹⁵³ This citation clearly shows that the chemical composition of the inorganic phases of bones was a hot topic of research in the 19th century.

In 1861, the presence of calcium orthophosphates in urine was investigated in further details,^{154,155} while the presence of calcium orthophosphates in the auditory system of mammals has been known since, at least, 1879.¹⁵⁶ The earliest journal paper I have been able to find, on a behavior of an undisclosed calcium orthophosphate in organisms of carnivores was published in 1883.¹⁵⁷

Concerning undesirable in vivo formed calcifications of biologically formed calcium orthophosphates, they have been known since, at least, 1809:¹⁵⁸ “The calculi found in the urethra consist of ammoniaco-magnesian phosphate, and phosphate of lime, with a small portion of uric acid” and “Mr. Brande, in the next section, has given the result of analysis of the calculi found in the horse, ox, sheep, rhinoceros, dog, hog, and rabbit. These were found mostly to consist of phosphate of lime and carbonate of lime in different proportions.”¹⁵⁸ Furthermore, let me cite a publication of 1814:¹⁵⁹ “Fusible Calculi. These are

composed chiefly of phosphate of lime, and the triple phosphate of Magnesia and Ammonia.” and “Bone-earth Calculi. These are composed chiefly of phosphate of lime.”¹⁵⁹

However, the earliest research paper I have been able to find on the undesirable calcifications was published in 1856,¹⁶⁰ followed by a book¹⁶¹ written by the famous German doctor, anthropologist, pathologist, prehistorian, biologist and politician Rudolf Ludwig Karl Virchow (1821–1902), in which he introduced a term “metastatic calcification.” To the best of my findings, next journal publications on undesirable in vivo formed calcifications containing calcium orthophosphates were in print in 1882¹⁶² and 1883.¹⁶³

Studies performed within 1900–1940. Research papers on the importance of calcium orthophosphates to bone health were kept publishing in 1906¹⁶⁴ and 1910.¹⁶⁵ Papers on the importance of calcium orthophosphates for lactation were published in 1914,¹⁶⁶ 1919¹⁶⁷ and 1922,¹⁶⁸ while the fact that the optimum Ca:P ratio in a diet is the same as that found in human bones or in mother’s milk has been known since at least 1930.¹⁶⁹

Research papers on undesirable in vivo formed calcifications were kept publishing in 1901,¹⁷⁰ 1906⁸⁰ and 1913.¹⁷¹ An important conclusion was made in 1906:⁸⁰ “The composition of the inorganic salts in calcified areas in the body seems to be practically the same, if not identical, whether the salts are laid down under normal conditions (ossification) or under pathological conditions.”⁸⁰ Thus, the similarity between the calcium orthophosphates of bones and those found in metastatic calcification has been known since at least 1906.

The next available studies on a behavior of an undisclosed calcium orthophosphate in organisms were in print in 1912¹⁷² and 1921.¹⁷³ A paper on the importance of calcium and phosphorus for growing children was published in 1913,¹⁷⁴ while that on the necessity of normal calcium and phosphorus metabolism was published in 1930.¹⁷⁵ Determination of the amounts of dissolved calcium orthophosphates in spinal fluid¹⁷⁶ and serum¹⁷⁷⁻¹⁷⁹ were performed in the 1920s, while that in saliva¹⁸⁰ and in serum of pregnant women^{181,182} and diseased people^{182,183} in the beginning of the 1930s.

To conclude this topic, one should mention a huge review published in 1935¹⁸⁴ and another one on bone composition published in 1937¹⁸⁵ summarizing the available by that time knowledge on calcium orthophosphates in living organisms.

Early Attempts to Treat Various Diseases by Calcium Orthophosphates

Attempts to treat various diseases by calcium orthophosphates have been known since at least 1804 and, initially, they were devoted to treat rickets:¹⁹ “In medicine it has begun to be prescribed in the Rachitis, to diminish the effects of acids which soften the bones, &c.”¹⁹ Further details became available by 1819:²² “Phosphate of lime has been employed as a remedy in rickets, a disease in which there appears to be a deficiency of this salt deposited in the bones. Its usefulness in this disease may be considered rather doubtful, unless the digestive powers of the system should be improved at the same time.”²²

However, the earliest journal articles, I have been able to find, were in print as early as 1851.^{186,187} The author performed a thorough study on the biomedical influence of phosphate of lime that was “taken with the breakfast, dinner, and supper, in order to have it mixed as well as possible with the food taken” on treatment of various diseases. According to the author:¹⁸⁶ “the phosphate of lime proved most beneficial in children who suffered from scrofula, diarrhoea, ulcerations and excoriations of the skin and the bowels, general waste of the cellular tissue, loss of power, &c. In these cases, the mere use of six to ten grains per diem was often quite sufficient to effect the cure, and I have met with such striking and satisfactory results, as to leave no doubt that the want of the phosphate of lime was the real cause of the symptoms alluded to.”¹⁸⁶ Furthermore, the author states: “As to other affections, in which I have tried the phosphate of lime, I have to mention rickets, caries, inflammations, and consecutive abundant suppurations of the cellular tissue, and also fractures of the bones. In all these cases, the administration proved most beneficial, and I would strongly advocate its further experimental use. With respect to fractures of the bones, I have to state in particular, that the consolidation of the callus took place in a much shorter period than is generally the case; however, too large doses of phosphate of lime must be shunned in these cases, as I have observed an abundant callus, causing a deformity of the bones, produced by the daily administration of twenty-four grains of the phosphate for a fortnight.”¹⁸⁶ In the second paper, the same author mentioned an interesting hypothesis that “phosphate of lime contained in a certain quantity of blood” (thus, the presence of calcium orthophosphates in blood was already known in 1851) might be partly “originated from the wear and tear of the bones and the muscular tissue.” Let me cite:¹⁸⁷ “Supposing now the wear and tear of bones to be abnormally increased, an abnormal quantity of phosphates will consequently re-enter into the composition of the blood, and by analysing the latter we shall find an increased quantity of phosphates in it. The general waste of bones is therefore leading to an increase of the phosphates in the blood, and nothing really would be more erroneous, than to suppose the general quantity of phosphates in the system to be increased, whenever we find their quantity increased in the blood.”¹⁸⁷ The readers are strongly advised to get through the both papers to rediscover the medical ideas and approaches published 160 years ago!

The next available medical study involving phosphate of lime was published in 1874.¹⁸⁸ An interesting idea to cure cancer “by embedding a piece of bone material or calcium phosphate in a cancer and exposing it to a pencil of X ray” to create a secondary radiation in calcium orthophosphates (either natural or implanted ones) was announced in 1913.¹⁸⁹ Strange enough, but seeking in the scientific databases on farther development of this idea has resulted in zero publications (researchers introduced radioactive isotopes of other chemical elements instead¹⁹⁰⁻¹⁹³). Nevertheless, this might be a worth reinvestigating approach.

The value of phosphorus and calcium in asthma, hay fever and allied diseases was investigated in 1928,¹⁹⁴ while the earliest paper, I have been able to find, on addition of calcium orthophosphates to forage of animals was published in 1953.¹⁹⁵

Artificial Grafts in the 19th Century and Before

The artificial generation of tissues, organs or even more complex living organisms was throughout the history of mankind a matter of myth and dream. Unfortunately, due to the practice of cremation in many societies, little is known about the prehistoric materials used to replace bones lost to accident or disease. Nevertheless, according to the available literature, introduction of non-biological materials into the human body was noted far back in prehistory. For example, the remains of a human found near Kennewick, WA USA (often referred to as the “Kennewick Man”) was dated to be up to 9,000 years old. This individual, described by archeologists as a tall, healthy, active person, wandered through the region now known as southern Washington with a spear point embedded in his hip. It had apparently healed in and did not significantly impede his activity. This unintended implant illustrates the body’s capacity to deal with implanted foreign materials. The spear point has little resemblance to modern biomaterials, but it was a tolerated foreign material implant, just the same.¹⁹⁶

Later, man’s attempts to repair the human body with the use of implant materials were recorded in the early medical writings of the Hindu, Egyptian and Greek civilizations. The earliest successful implants were in the skeletal system. Namely, applying modern pathology methods to a ~3,000-y-old mummy, researchers at Ludwig Maximilians University, Munich, showed that ancient Egyptian physicians designed wooden prostheses to help their ailing patients: in that case, a 50–60-y-old woman whose toe was amputated (Fig. 2).¹⁹⁷ Besides, the famous painting by Fra Angelico (ca. 1395–1455) “The Healing of Justinian by Saint Cosmas and Saint Damian” (Fig. 3) a visualization of the legend of twins Sts. Cosmas and Damian (died ca. 287 AD) depicting a transplantation of a homograft limb onto an injured soldier, is one early instance of the vision of a regenerative medicine.

Historically, a selection of the materials was based on their availability and an ingenuity of the individual making and applying the prosthetic.¹⁹⁸ Archaeological findings exhibited in museums showed that materials used to replace missing human bones and teeth included animal or human (from corpses) bones and teeth, shells, corals, ivory (elephant tusk), wood (Fig. 2), as well as some metals (gold or silver). For instance, the father of Western medicine Hippocrates (ca. 460–370 BC) apparently used gold wire and linen thread for ligatures in the repair of bone fractures. Aulus Cornelius Celsus (ca. 25 BC–50 AD) recommended the filling of large cavities with lint, lead and other substances before attempting extraction to prevent the tooth from breaking under the pressure of the instrument. This may have been the beginning of filling materials for carious teeth. The Etruscans learned to substitute missing teeth with bridges made from artificial teeth carved from the bones of oxen, while in ancient Phoenicia loose teeth were bound together with gold wires for tying artificial ones to neighboring teeth. Popp states that ancient Egyptians also made artificial ears, noses and eyes.¹⁹⁹ The Chinese recorded the first use of dental amalgam to repair decayed teeth in the year 659 AD, while in the Americas the pre-Columbian civilizations used gold sheets to heal cranial cavities following trepanation.²⁰⁰ Besides, while excavating Mayan burial sites in Honduras in 1931,

archeologists found a fragment of mandible of Mayan origin, dating from about 600 AD. This mandible, which is considered to be that of a woman in her twenties, had three tooth-shaped pieces of shell placed into the sockets of three missing lower incisor teeth. In 1970, a Brazilian dental academic Prof Amadeo Bobbio studied the mandible specimen and took a series of radiographs. He noted compact bone formation around two of the implants, which led him to conclude that the implants were placed during life.²⁰¹ This may be the first recorded use of dental implants. More to the point, an iron dental implant in a corpse dated ~200 AD was found in Europe. This implant, too, was described as properly bone integrated.²⁰²

In middle ages, one of the first scientific descriptions of congenital and acquired defects of the maxilla and their treatments was given by Ambroise Paré (1510–1590) in his *Dix livres de la chirurgie, avec le magasin des instrumens necessaires à icelle*, published in Paris in 1564. He specifically described defects of the palate with bone destruction caused by arquebus shots, stab wounds or syphilitic gumma, describing also the accompanying speech deficiency and giving general principles of treatment. He used a flat, vaulted, metallic plate in gold or silver with a sponge attached to it. The sponge was introduced into the defect, where it expanded with readily absorbed nasal and oral secretions, thus holding the obturator base in position. Paré is also credited with having prepared artificial teeth from bones and ivory. In the 17th century, a piece of dog skull was successfully transplanted into the damaged skull of a Dutch duke.

In the 18th century, a common method to replace teeth was the homologous transplantation of teeth in humans. John Hunter (1728–1793) investigated in his pioneering work the effect of transplantation not only at a clinical level (he claimed that homologous transplanted teeth lasted for years in the host) but also performed animal experimental work on the fate of transplants, thereby setting the basis for a scientific approach on transplantation medicine.²⁰³ Besides, various restorative materials might be used for feeling defects, capping exposed pulps and dental cavities. Currently they include zinc orthophosphate, zinc polyacrylate (polycarboxylate), various amalgams, glass ionomer cement of complicated formulations, calcium hydroxide, etc.; however, this is another story. Within the scope of this review, calcium orthophosphate-based formulations will be considered only. According to the available literature, Dr Junius E. Cravens (1844–1920) from the US proffered creative concepts in pulp capping in the 1870s. He had the opinion that dentin-like material would be the best to keep the pulp vital. Therefore, Cravens used a calcium orthophosphate powder, which was mixed with lactic acid to low viscosity. The result was a soluble calcium lactic orthophosphate, which was applied onto the exposed pulp tissue.²⁰⁴ This pulp-capping agent was brought to the market by the S.S. White company with the trade name “Lacto-Phosphate of Lime” (Fig. 4). Sugar-containing formulations were known as well.²⁰⁵ To the best of my findings, the study by Cravens might be considered as the first mentioning on artificial calcium orthophosphate-based biocomposites and hybrid biomaterials (reviewed in reference 206). Thus, one might claim that the grafting history of calcium orthophosphates started in 1870s.



Figure 2. A wooden prosthesis of a hallux of a mummy. Reprinted with permission from Jacoby M.¹⁹⁷



Figure 3. Fra Angelico (ca. 1395–1455) “The Healing of Justinian by Saint Cosmas and Saint Damian” (approximately 1439) is exhibited at Museo di San Marco, Florence, Italy.

One must stress that in the past, many implantations failed due to various infections, which tended to be exacerbated in the presence of implants, since they provided a region inaccessible

LACTO-PHOSPHATE OF LIME.

This article has been recommended by Dr. J. E. Cravens for the treatment of sensitive dentine, and to promote deposition of dentine in exposure of pulps.

Put up in half-ounce bottles, in the form of paste, ready for application.

Price..... 50 cents.

SAMUEL S. WHITE.

Figure 4. An advertisement of the S.S. White company for “Lacto-Phosphate of Lime” 1873. Reprinted from Dent. Cosmos.²⁷⁷

Table 2. The chemical composition of two bone samples taken from a publication of 1871³⁸

	Commercial bone-ash	Pure ox bone-ash
Moisture and volatile matter	6.70	1.86
Siliceous matter	9.69	0.51
Oxide of iron	0.58	0.17
Lime	43.37	52.46
Magnesia	1.14	1.02
Phosphoric acid	33.68	39.55
Carbonic acid, alkalies, and other substances undetermined	4.84	4.43
Total	100.00	100.00

to the body’s immunologically competent cells. Thus, the use of implantable biomaterials did not become practical until the advent of an aseptic surgical technique developed by a British surgeon Sir Joseph Lister (1827–1912) in the 1860s. Furthermore, there was a lack of knowledge about a toxicity of the selected materials. The exact chemical composition of the normal calcified tissues of mammals has been known since, at least, 1870, which might be concluded from both Table 2³⁸ and the following citations: “The bones and teeth of animals contain large amounts of calcium phosphate, together with some carbonate and fluoride”⁵⁵ and “Calcium phosphate is also the chief inorganic constituent of bones, forming about 80 per cent of burnt bones; the other constituents being magnesium phosphate, calcium carbonate, and calcium fluoride.”⁵⁵ Those data were updated in 1894.²⁰⁷ However, the apatitic structure of the calcium orthophosphates of bones and teeth has been established by X-ray diffraction in 1926²⁰⁸ and confirmed in 1932²⁰⁹ and 1933.²¹⁰ Since that time, bone mineral has been frequently identified as HA. In this frame, application of calcium orthophosphates as artificial grafts appears to be logical due to their similarity with the mineral phases of bones and teeth.

To conclude this topic, one should stress that the performance of living tissues is the result of millions years of evolution, while the performance of acceptable artificial substitutions those humankind has designed to repair damaged tissues are only a few decades old. This explains the greatest differences between them. To get the historical perspective on the development of artificial grafts prepared from other materials, the interested readers are referred to the special literature.^{6,8-11,211-214}

Calcium Orthophosphates as Bone Graft Substitutes: A Historical Perspective

Historically, plaster of Paris (calcium sulfate) was the first widely tested artificial bioceramics. For example, according to Wikipedia, the free encyclopedia, literature dating back to 975 AD notes that calcium sulfate was useful for setting broken bones. However, those were ex vivo applications. According to the available literature, by the end of the 19th century, surgeons already used plaster of Paris as a bone-filling substitute.²¹⁵ Nevertheless, it was a famous German surgeon Themistocles Gluck (1853–1942), who, among his range of contributions, on May 20, 1890 performed the first well documented ivory (virtually, pure biological apatite) knee replacement bedded in a calcium sulfate based cement, which was followed by a total wrist replacement in another patient three weeks later.²¹⁶ Later in 1890, Gluck presented a further case of a total knee replacement to the Berlin Medical Society: at only 35 days after operation, the patient was pain free with active knee flexion and extension. All the joint arthroplasties performed by Gluck were remarkably successful in the short-term; however, all ultimately failed because of chronic infections.^{217,218} After the above-mentioned case of lacto-phosphate of lime (Fig. 4), this seems to be the second well-documented grafting application of calcium orthophosphates.

However, in the aforementioned cases, either the biomedical applications of biologically produced calcium orthophosphates (Gluck) or dental applications, not requiring any surgery (Cravens) have been described. According to both the electronic databases and previous reviews on the subject,^{6,8-11,211-214} the first attempt to implant a laboratory produced calcium orthophosphate (it was TCP) as an artificial material to repair surgically created defects in rabbit bones was performed in 1920⁷ by an US surgeon Fred Houdlette Albee (1876–1945), who invented bone grafting²¹⁹ and some other advances in orthopedic surgery. The researchers injected either 0.5 or 1 cc of 5% slurries of TCP in distilled water (which was then sterilized for three successive days in the Arnold sterilizer, at 60°C) into surgically created radial bone gaps of rabbits, leaving the periosteum intact.⁷ Radiographic analysis revealed that the TCP injected defect demonstrated more rapid bone growth and union than the control. The average length of time for bony union with TCP was 31 days, compared with 41 days for the controls. No appreciable bone growth was stimulated by injecting TCP beneath the periosteum in non-defective radii or into subcutaneous tissues. Although this seems to be the first scientific study on use of an artificially prepared calcium orthophosphate for in vivo repairing of bone defects, it remains unclear whether that TCP was a precipitated or a ceramic material and whether it was in a powder or a granular form. Unfortunately, the researchers published nothing further on this topic. In 1927, Hey Groves (1872–1944) described pure ivory hip hemiarthroplasty for fracture.²²⁰ In 1931, Murray also reported an acceleration of healing following implantation of calcium salts composed of 85% TCP and 15% CaCO₃ in canine long bone defects.^{221,222}

At the beginning of the 1930s, the classic osteoinductive phenomenon was defined well by Huggins,²²³ who demonstrated that autoimplantation of transitional epithelium of the urinary bladder to abdominal wall muscle in dogs provoked ectopic bone formation. A bit later, Levander demonstrated that crude alcoholic extracts of bones induced a new bone formation when injected into muscle tissue.^{224,225}

Simultaneously, in the 1930s, Haldeman and Moore,²²⁶ Stewart,²²⁷ Key²²⁸ and Shands²²⁹ discovered the fact that only certain types of calcium orthophosphates mentioned in Table 1 really influence the bone healing process. Namely, Haldeman and Moore implanted various calcium orthophosphates such as MCP and DCP (it remains unclear whether they were in hydrated or anhydrous forms), TCP, as well as calcium glycerophosphate as dry powdered salts into 0.5 to 1.0 cm defects in radii of 17 rabbits, while the opposite side served as control. Radiographic analysis demonstrated that in no case did the presence of MCP, DCP or calcium glycerophosphate had a favorable influence delayed healing compared with control, while the presence of TCP at the site of the fracture appeared to favor the union.²²⁶ Furthermore, Key²²⁸ suggested that “if a defect in bone could be filled by a non-irritating, slowly soluble mass, which was porous and which contained calcium phosphate and carbonate in a form in which they could be resorbed, it would be reasonable to expect osteoblasts to invade the mass, utilize the calcium, and build new bone which would replace the mass of calcium and cause the bone to be restored to its original form. The ideal material would appear to be rather dense cancellous bone from which a large percentage of the organic material had been removed.”²²⁸ However, Key found that “Neither calcium phosphate and carbonate in the proportions in which they occur in bone, nor bone powder, made by removing the organic matter from bone, appear to stimulate osteogenesis of bone when implanted in a bone defect.”²²⁸ Stewart²²⁷ concluded that “1. Lime salts and boiled bone when placed into a bone defect with either traumatized muscle or fascia do not serve as a source of available calcium resulting in supersaturation of connective tissue and regeneration of missing bone. 2. Live bone chips placed in bone defects regenerate the missing bone.”²²⁷ Shands²²⁹ also reported conflicting effects of several calcium salts [calcium glycerophosphate, a mixture of TCP (3 parts) and CaCO₃ (1 part), bone ash and calcium gluconate] on bone repair. Namely, in defects in the ulna of dogs, the investigated calcium salts appeared to stimulate bone formation, while in operations upon the spine, calcium glycerophosphate did not stimulate bone formation and appeared rather to exert an inhibiting influence. In 1948, Schram and Fosdick confirmed the fact that only certain types of calcium orthophosphates influence the bone healing process.²³⁰ Similar conclusions were obtained in 1951 by Ray and Ward.²³¹

Due to the reasons mentioned in the abstract, more recent historical events are reported very briefly. Namely, in 1950 the history of calcium orthophosphate cements was started.²³² The author of that important publication investigated mixtures of both oxides and hydroxides of various metals with aqueous solutions of orthophosphoric acid and discovered a number of

cold-setting formulations. For example, he found that CaO, sintered at 1100°C, did not set in H₃PO₄, while that in liquid containing 9.6% CaO was found to set after ~12 h in the presence of H₃PO₄.²³² The latter mixture might be considered as the first prototype of self-setting calcium orthophosphate cements (reviewed in refs. 233 and 234). The next publication on this subject appeared in 1975;²³⁵ however, the real history of the self-setting calcium orthophosphate cements started in 1982.^{236,237}

The modern history of ACP³⁴ started in 1955,²³⁸ while more than 20 years afterwards the first dental application of a calcium orthophosphate (erroneously described as TCP) in surgically created periodontal defects²³⁹ and the use of dense HA cylinders for immediate tooth root replacement²⁴⁰ were reported. According to the available databases, the first paper with the term “bioceramics” in the abstract was published in 1971,²⁴¹ while with that in the title were published in 1972.^{242,243} However, application of the ceramic materials as prostheses had been known before.²⁴⁴⁻²⁴⁷ On April 26, 1988, the first international symposium on bioceramics was held in Kyoto, Japan.

The history of calcium orthophosphate based biocomposites and hybrid biomaterials (reviewed in ref. 206) started in 1981, while that of calcium orthophosphate coatings (reviewed in refs. 248 and 249) started in 1980.²⁵⁰ An extensive commercialization of the dental and surgical applications of calcium orthophosphate (mainly, HA) bioceramics occurred in the 1980s, largely due to the pioneering efforts by Jarcho²⁵¹⁻²⁵⁴ in the US, de Groot²⁵⁵⁻²⁵⁷ in Europe and Aoki²⁵⁸⁻²⁶¹ in Japan. Shortly afterwards HA has become a bioceramic of reference in the field of calcium orthophosphates for biomedical applications. Preparation and biomedical applications of apatites derived from sea corals (coralline HA)²⁶²⁻²⁶⁴ and bovine bone²⁶⁵ have been reported at the same time,²⁶⁶ while the history of biphasic, triphasic and multiphasic calcium orthophosphates (reviewed in ref. 267) started in 1985.^{268,269} Finally yet importantly, the history of nanodimensional and nanocrystalline calcium orthophosphates (reviewed in refs. 270 and 271) started in 1994.²⁷²⁻²⁷⁶

To get further details on a recent history of calcium orthophosphates, bioceramics and biomaterials in general, the interested readers are referred to other reviews on the subject.^{6,8-11,211-214}

Conclusions

The reported historical findings clearly demonstrate that the subject of calcium orthophosphates have been investigated for almost two and a half centuries. Furthermore, the substantial amount of both scientific facts and experimental approaches has been known for very many decades and, in fact, the considerable quantity of relatively recent investigations on calcium orthophosphates is just either a further development of the earlier studies or a rediscovery of the already forgotten knowledge. Nevertheless, first commercially produced bone grafts and other types of biomaterials consisting of calcium orthophosphates appeared just a few decades ago.²⁵¹⁻²⁶¹ Furthermore, the biomedical properties of even the most advanced formulations are still unsatisfactory and incomparable with those of natural bones and teeth. However, the advantages and obvious benefits of calcium orthophosphates

remain both an inspiration and a hope of many researchers and clinicians. Hopefully, the reported historical overview will keep encouraging both natural scientists and clinicians to rethink and

reinvestigate the already forgotten and poorly known facts and approaches in further development of calcium orthophosphates and calcium orthophosphate-based formulations.

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