Chapter 15

History of Calcium Phosphates in Regenerative Medicine

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Abstract The historical development of a scientific knowledge on calcium orthophosphates from the 1770s until 1950 is described. The chosen time scale starts with the earliest available studies of the 1770s (to the best of my findings, calcium orthophosphates had been unknown before), passes through the entire nineteenth century, and finishes in 1950, because since then the amount of publications on calcium orthophosphates rapidly increased and the subject became too broad. In addition, since publications of the second half of the twentieth century are easily accessible, the substantial amount of them has been already reviewed by other scientists. Many forgotten and poorly known historical facts and approaches have been extracted from the old publications. Then they have been analyzed, systematized, and reconsidered from the modern point of view. The reported historical findings clearly demonstrate that many famous scientists of the past contributed to calcium orthophosphate investigations. Furthermore, the significant quantity of the scientific facts and experimental approaches appears to have been known for very many decades, and, in fact, a good deal of the relatively recent investigations on the subject is just either a further development of the earlier studies or a rediscovery of the already forgotten knowledge.

Keywords Apatite • Calcium orthophosphate • Lime phosphate • Calcium phosphate • Calcareous phosphate

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15.1 Introduction

By virtue of abundance in the nature and presence in the living organisms, calcium orthophosphates (Table 15.1) appear to be the chemical compounds of a special interest in many fields of science, including geology, chemistry, biology, and medicine [1, 2]. As seen from Table 15.1, calcium orthophosphates with the Ca/P ratio within 1.5–1.67 are called apatites (hydroxyapatite, fluorapatite, and oxyapatite). As a mineral species, apatite was first recognized in 1786 by “the father of German geology” Abraham Gottlob Werner (1750–1817) and named by him from the ancient Greek απατάω (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. However, in this review, the term “apatite” is referred to calcium orthophosphates only and means CDHA, HA, FA, and OA (Table 15.1).

As follows from the designation, all calcium orthophosphates contain both calcium (Ca, atomic number 20) and phosphorus (P, atomic number 15) as the major constituencies. The history of both chemical elements is long. Namely, 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 [3]. 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 [4, 5].

Phosphorus is a bit younger. The discovery of this 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 the German merchant and alchemist Hennig Brand (ca. 1630–ca. 1710) in 1669, although other alchemists might have discovered phosphorus around the same time. Brand experimented with urine, which contained considerable quantities of dissolved phosphates from the normal metabolism [6]. As the matter stands, the earliest research publication containing the word “phosphorus” in the title belongs to M. Krafft from Holland and was printed in 1677 in French *Journal des Sçavans* [7], which was the earliest academic journal published in Europe. In 1680, the famous British natural philosopher, chemist, physicist, and inventor Robert Boyle (1627–1691) also deposited a paper on phosphorus, but it was published only in 1693, shortly after his death [8]. However, it was the famous French chemist Antoine Laurent Lavoisier (1743–1794) who recognized phosphorus as a chemical element in 1777. It turns out that phosphorus was the first element discovered since antiquity [6].

Table 15.1 Existing calcium orthophosphates and their major properties

Ca/P molar ratio	Compounds and their typical abbreviations	Chemical formula	Solubility at 25 °C, $-\log(K_s)$	Solubility at 25 °C, g/L	pH stability range in aqueous solutions at
0.5	Monocalcium phosphate monohydrate (MCPM)	$Ca(H_2PO_4)2{\cdot}H_2O$	1.14	~18	0.0–2.0
0.5	Monocalcium phosphate anhydrous (MCPA or MCP)	$Ca(H_2PO_4)_2$	1.14	~17	[c]
1.0	Dicalcium phosphate dihydrate (DCPD), mineral brushite	$CaHPO_4{\cdot}2H_2O$	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)	$Ca_8(HPO_4)_2(PO_4)_4{\cdot}5H_2O$	96.6	~0.0081	5.5–7.0
1.5	α-Tricalcium phosphate (α-TCP)	$\alpha\text{-}Ca_3(PO_4)_2$	25.5	~0.0025	[a]
1.5	β-Tricalcium phosphate (β-TCP)	$\beta\text{-}Ca_3(PO_4)_2$	28.9	~0.0005	[a]
1.2–2.2	Amorphous calcium phosphates (ACP)	$Ca_xH_y(PO_4)_z{\cdot}nH_2O$, $n = 3–4.5$; 15–20 %	[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)	$Ca_{10}(PO_4)_6F_2$	120.0	~0.0002	7–12
1.67	Oxyapatite (OA, OAp or OXA)[f]	$Ca_{10}(PO_4)_6O$	~69	~0.087	[a]
2.0	Tetracalcium phosphate (TTCP or TetCP), mineral hilgenstockite	$Ca_4(PO_4)_2O$	38–44	~0.0007	[a]

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[a] These compounds cannot be precipitated from aqueous solutions

[b] Cannot be measured precisely. However, the following values were found: 25.7 ± 0.1 (pH = 7.40), 29.9 ± 0.1 (pH = 6.00), and 32.7 ± 0.1 (pH = 5.28). The comparative extent of dissolution in acidic buffer is ACP $\gg$ α-TCP $\gg$ β-TCP > CDHA $\gg$ HA > FA

[c] Stable at temperatures above 100 °C

[d] Always metastable

[e] Occasionally, it is called “precipitated HA (PHA)”

[f] Existence of OA remains questionable

15.2 General Definitions, Major Problems, and Limitations

To begin with, one must define the subject and outline the problems. According to Wikipedia: “History (from Greek ἱστορία – historia, meaning “inquiry, knowledge acquired by investigation”) is the discovery, collection, organization, and presentation of information about past events. It is a field of research which uses a narrative to examine and analyse the sequence of events, and it sometimes attempts to investigate objectively the patterns of cause and effect that determine events. The task of historical discourse is to identify the sources which can most usefully contribute to the production of accurate accounts of past” [9].

Unfortunately, the requirement “to identify the sources” meets serious problems, due to the substantial difficulties with accessing to the scientific literature published in the first half of the nineteenth century and before. In addition, that time, both the scientific concepts and the presentation ways were rather different from the modern ones, while the chemical formulae had not been introduced yet. More to the point, scientific journals were rare and just a few of them are currently available in the electronic form. To complicate things further, numerous old journals have been discontinued, merged, and/or renamed, which strongly complicates accessing to the papers published in those journals. Luckily, Google Inc. has scanned a great number of old books 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 Driskell entitled “Early history of calcium phosphate materials and coatings” [10] started with the classical publication of 1920 by Albee assisted by Morrison [11]. In 1999, Shackelford published a paper, “Bioceramics – an historical perspective” [12], in which the same publication by Albee assisted by Morrison [11] was mentioned as the earliest reference. The same is valid for the historical papers by Hulbert et al. [13, 14] and Shepperd [15]. 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 that happened in the first half of the nineteenth century still remains poorly restorable, while the correct historical time scale of even earlier scientific events remains almost irrecoverable. This is mainly due to a lack of the citation practice existing in the scientific literature published at that time. Besides, even nowadays, for the entire eighteenth century and approximately the first quarter of the nineteenth century, only scientific books digitalized by Google are easily accessible. Just a few journal papers devoted to the subject published before $\sim$1820s have been found. Nevertheless, in no case this means that they do not exist; presumably, either they have not been scanned yet (especially, this might be valid for the discontinued journals) or an access to the scanned versions is restricted to a limited amount of subscribers only. Therefore, the historical narrative of the findings and discoveries of the eighteenth century is based dominantly on the available books, and the annals of the nineteenth century are based on both the available books and a limited number of journal papers, while the chronicle of the twentieth century is based on the journal publications only. Here one should also stress that starting from the second half of the nineteenth century, the detailed description of every publication on the subject becomes impossible due to permanently increasing amount of them. Furthermore, since the end of the 1910s, even mentioning all and sundry publications on the subject becomes impossible either (the quantity with moderate novelty breeds ignoring). Therefore, for the twentieth century, the milestone studies have been included only.

15.3 Investigations and Knowledge at the “Pre-calcium Orthophosphate” Time

Prior examination of issues let me briefly report on the earliest scientific publications on bones, teeth, and other types of calcified tissues of mammals, which are the main sources of calcium orthophosphates of the biological origin. Since in those early days the major scientific language was Latin, I am forced to confine myself by the English-language publications only.

According to the second earliest but the world’s longest-running scientific journal *Philosophical Transactions* (published in UK), the priority in journal publications on investigations of bones and teeth belongs to the famous Dutch tradesman and scientist Antonie Philips van Leeuwenhoek (1632–1723) from Delft. He is best known for his work on the improvement of a microscope and is often considered as “the father of microbiology.” Therefore, within 1674–1695, van Leeuwenhoek published several letters devoted to microscopic investigations of bones and teeth [16–20]. Namely, he wrote (please note the old-fashioned using 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) [16]: “I thought likewiſe, I ſaw then alſo, that that Bone conſiſted of united Globuls. Afterwards, I viewed the Shinbone of a *Calf*, in which I found ſeveral little holes, paſſing from without inwards; and I then imagined, that this Bone had divers ſmall pipes going longways” (p. 125). Today these small pipes are known as Haversian canals, named after the British physician Clopton Havers (1657–1702), who did the pioneering research on the microstructure of bones and teeth [21]. Let me continue citing [16]: “But I have ſince obſerved the *Tooth* of a Cow and I found it made up of tranſparent Globuls which I can ſee very perfectly. The ſame I have obſerved in *Ivory* or *Elephants-Teeth*. And having ſeen this ſeveral times, I doubt no longer but that all white Bones do conſiſt of tranſparent Globuls” (p. 125). Obviously, this was the first recognition of the fact that bones and teeth of mammals consist of small units (currently we call them crystals) with a transparent nature. Indeed, single crystals of all known calcium orthophosphates (Table 15.1) are transparent.

Simultaneously, other researchers tried to measure the physical properties and establish the chemical composition of various calcified tissues (both normal and pathological) of humans. For example, let me cite a summary of the experiments performed by the British physician and chemist Frederick Slare (1648–1727) from a publication of 1684 [22]: “Several *Stones* of the *Bladder* and *Kidnies* were diſtill’d, all afforded *volatile urinous Salts*; which *Ferment* upon any *Acids. Bones* were diſtill’d and found to be of agreeable *Principles. Calculi* examined *Hydroſtatically*, were found in proportion to their Bulk of water as 5 to 4. We weigh’d *Bones Hydroſtatically* and found them twice as heavy as their Bulk of water. *Bones* not eaſily wrought on by common *Acids*, only by nitrous ones and that without *Ebullition*.” (p. 532). Therefore, scientists dissolved biologically formed calcium orthophosphates in acids as far back as 1684.

Shortly before a discovery of the calcium orthophosphate nature of bones (the next section), Hérissant (presumably, it is referred to either Jean Thomas Hérissant or his son Louis Antoine Prosper Hérissant) and the Swiss anatomist, physiologist, naturalist, and poet Albrecht von Haller (1708–1777) examined a phenomenon that even the weakest acids had the power of softening bones. Namely, according to Fourcroy [23], that study was reported in 1758 and Hérissant “thought he had found in the nitric acid (with which he ſoftened the bones which he ſoaked in it, by diſſolving their earth, which he believed to be cretaceous, without affecting their membraneous cellular part) a means of inſulating the two conſtituent matters of theſe organs. Haller has verified this ſoftening of the bones even by the acetous acid and lemon juice; he ſuſpected that in the ſoftening of the bones by the effect of diſeaſes, there exiſted an acid which thus corroded them. All the chemiſts have afterwards obſerved that a ſolution of bones in an acid precipitated by alkali affords a ſeemingly earthy matter, which does not poſſeſs the property of becoming quicklime by calcination.” (p. 388).

To conclude this part, one can see that the aforementioned few examples clearly demonstrate a scientific importance of the “pre-calcium orthophosphate” epoch, which, ideally, should be investigated in more details. Undoubtedly, one must appreciate the important observations and discoveries made by those early researchers-predecessors.

15.4 Investigations and Knowledge on Calcium Orthophosphates

15.4.1 In the Eighteenth Century

According to the available literature, the history of calcium orthophosphates began in 1769 and was associated with names of the famous Swedish chemist and metallurgist Johan Gottlieb Gahn (1745–1818) and the famous German-Swedish pharmaceutical chemist Carl Wilhelm Scheele (1742–1786). Namely, in 1881, Roscoe and Schorlemmer [24] 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" (p. 458). Furthermore, let me cite a publication of 1777 [25] (again, pay attention to the old-fashioned using a letter "ſ" instead of "s"): "I have only been informed of this diſcovery, by the *Gazette*, *Salutaire 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." (p. 383). Presumably, this citation might be considered as one of the earliest mentioning on calcium phosphates in the history.

The earliest accessible description on how Scheele discovered the chemical composition of bones was given by Fourcroy in 1804 [23]: "After having, like Heriſſant, diſſolved bones in the nitric acid, he filtrated the liquor, and aſcertained that, though always acid, even when ſaturated with all that it could diſſolve of bone, it precipitated ſulphate of lime by the addition of concentrated ſulphuric acid; and that after this precipitation, the ſolution drawn off clear, and evaporated in a retort, afforded volatilized nitric acid, and left phoſphoric acid, which was fuſed into glaſs by the action of a ſufficient heat. He concluded from this experiment that the nitric acid diſſolved the phoſphate of lime, the baſe of the bones; that the ſolution in this acid was a mixture of calcareous nitrate and of phoſphoric acid; that when the firſt was decompoſed by the ſulphuric acid, and the precipitated ſulphate of lime ſeparated from it, there remained only a mixture of the two acids, the phoſphoric and the nitric, and that this latter mixture, when heated, diſengaged volatile nitric acid, whilſt the fixed phoſphoric acid remained at the bottom of the retort." (pp. 388–389). Even more than 200 years afterward, we can add nothing to improve this description. This is an example of how the genius could do!

Simultaneously, the presence of orthophosphates was discovered in blood serum, which follows from a publication of 1770 [26]: "The ſerum conſiſts chemically of a coagulable matter, and water in which common ſal ammoniac and phoſphoric ammoniac, and generally common ſalt, and frequently ſelenites, and, fixed ammoniac, are diſſolved" (p. 309). Obviously, "phoſphoric ammoniac" means ammonium orthophosphate.

Further, according to Shepperd [15], the famous German chemist Martin Heinrich Klaproth (1743–1817) and the famous French chemist Joseph-Louis Proust (1754–1826) also contributed to 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 given some results. For example, a short extract from a letter by M. Klaproth was published in 1788 [27], which started with the following words: "Monsieur, Je viens d'analyſer l'apatit de M. Verner (I). J'en ai retiré de la terre calcaire & de l'acide phoſphorique" (p. 313). In addition, in a French book of 1790 [28], 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" (p. 363). 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" (p. 366). Thus, by that time, apatite was already recognized as a calcium phosphate, which is also confirmed by a German book of 1789 [29], in which "Apatit" was called "die Phosphorsaure mit Kalkerde" (p. 2).

More to the point, according to a study, submitted on December 20, 1785 [30], the production process of orthophosphoric acid by decomposition of calcined bones in sulfuric acid was already known. This is how it was described by Lavoisier in 1790 [31]: "The bones of adult animals being calcined to whteneſs, are pounded, and paſſed through a fine ſilk ſiewe; 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." (p. 205). Further, the production process of white phosphorus has been described [31]: "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." (p. 206).

In the last decade of the eighteenth century, very extensive 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, among other accomplishments, discovered an existence of acidic calcium orthophosphates, currently known as MCPM, MCPA, DCPD, and DCPA (Table 15.1). For example, let me cite a Fourcroy's book of 1789 [32]: "Phoſphoric acid, poured into lime-water, precipitates from it a ſcarce ſoluble ſalt, which does not efferveſce with acids, – is decompoſed by mineral acids, but proof againſt the attacks of cauſtic alkalis. This ſalt is of the ſame nature with the baſe of bones. An exceſs of phoſphoric acid renders calcareous phoſphate ſoluble in water; but magneſia, lime, cauſtic fixed alkalis, and even ammoniac, by carrying off from it the exceſs of acid, precipitate the neutral ſalt. Calcareous phoſphate is not decompoſable by caustic alkalis, but carbonates of potaſh and ſoda decompoſe it. The ſolid matter of bones conſiſts of phoſphate ſuperſaturated with lime." (p. 248). Here we read the correct chemical description of CDHA precipitation from H_3PO_4 and $Ca(OH)_2$, followed by CDHA transformation into soluble MCPM in the presence of an excess of H_3PO_4, which is again transformed into insoluble CDHA by addition of basic compounds MgO, CaO, KOH, NaOH, and NH_4OH. Moreover, the last sentence means that the amount of CaO in bones exceeds the stoichiometry of orthophosphates; therefore, that was the earliest indirect observation of the apatitic ($Ca/P > 1.5$) composition of bones.

Furthermore, in his later book of 1804 [33], Fourcroy wrote: "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." (p. 347). The aforementioned is confirmed by an encyclopedia published in 1816 [34]: "*Super*-Phosphat of Lime was diſcovered in 1795, by Fourcroy and Vauquelin. It had indeed been often formed before, but chemiſts had neglected to examine it" (p. 458). Thus, the term "superphosphate" has been known since, at least, 1795, and initially it meant calcium phosphates containing an excess (or super quantity) of phosphoric acid. Besides, in the same publication, Fourcroy mentioned other contributors to early studies on calcium orthophosphates [33]: "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" (p. 337). Thus, one can notice that in the end of the eighteenth century, the subject of calcium orthophosphates was extensively investigated by a number of researchers in several countries of Western Europe.

Finally, it is important to cite a page from an agricultural chemistry book, published in 1795 [35]: "PHOSPHAT OF LIME Is contained in animal matters, such as bones, urine, shells, &c. &c. in some sorts of limestone, and in vegetable substances, particularly in the gluten, or vegeto-animal matter of wheat or other grain. It is a saline compound very insoluble. There is reason to believe, a very considerable proportion of this nearly insoluble salt is contained in most fertile soils, especially those that have been long under cultivation. It is not to be decomposed by pure alkalis; but this may be effected by mild vegetable and mineral alkalis, on the principle of the double electrive attractions; in which case, carbonate of lime (or chalk) will be precipitated, and phosphoric acid will join with the alkali, and form phosphat of potash, or phosphat of soda, according to the alkali applied. These alkaline phosphates will be found to promote vegetation in a very great degree: the substances of which they are composed, viz. alkaline salts and phosphoric acid, are found in the ashes of most vegetables." (p. 75)

To conclude the 1700s, one should recognize that the correct basic knowledge on calcium orthophosphates became available by the end of the eighteenth century.

15.4.2 In the Nineteenth Century

For the nineteenth century, both scientific books and a limited amount of journal publications are available; however, for the first half of the nineteenth century, the quantity of journal publications was very small. Nevertheless, according to the available literature, one can claim on a real explosion of the scientific knowledge on calcium orthophosphates in the nineteenth century. For example, in 1804, Fourcroy stated that the presence of water in acidic calcium orthophosphates was already known (again, pay attention to the old-fashioned using a letter “ſ” instead of “s”) [33]: “The acid phoſphate of lime contains a remarkable quantity of water: the cryſtallization immediately ſoftens and becomes liquefied by the fire” (p. 349). The chemical compositions of both neutral and acidic calcium orthophosphates were described as follows [33]: “100 parts of phoſphate of lime contain, according to the analyſis of Citizens Fourcroy and Vauquelin,

Phoſphoric acid	41
Lime	59” (p. 346),

and “An accurate analyſis of this ſalt affords the following proportions of component parts,

Lime	45
Phoſphoric acid	54” (p. 351).

Unfortunately, it is impossible to establish the real meaning of all numerical values. Nevertheless, if we consider the first compound as the stoichiometric HA (Ca/P = 1.67), simple calculations using the proportion rules will give Ca/P = 0.96 for the acidic phosphate of lime, and if we consider the first compound as TCP (Ca/P = 1.50), similar calculations will give Ca/P = 0.86 for the acidic phosphate of lime. In both cases, the calculated Ca/P ratios appear to be close to those in DCPD and DCPA. Taking into consideration that the “acid phoſphate of lime contains a remarkable quantity of water,” one can conclude that Fourcroy prepared DCPD by 1804. Finally, one more citation from Fourcroy’s book is as follows [33]: “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” (p. 341). Thus, calcium phosphate ceramics were prepared by 1804.

Knowledge on acidic calcium orthophosphates was further developed in 1805 [36], “*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” (p. 195), and in 1806 [37], “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” (p. 38). In 1807, a detailed preparation technique of superphosphate of lime was described as follows [38]: “This ſuper-phosphat of lime is prepared with moſt accuracy by digesting phoſphat of lime in phoſphoric acid till it is ſaturated. This ſolution yields the ſalt by evaporation in the form of ſmall ſhining seales or filaments which have almost a gelatinous conſiſtence, and a very ſour taſte” (p. 222). Obviously, this was the earliest description of MCPM preparation; however, an admixture of MCPA was possible due to a partial dehydration at the evaporation stage.

More precise information on acidic calcium orthophosphates became available by 1819 [39]: “XI. *Biphosphate of Lime*. This salt may be formed by digesting phosphate of lime in phosphoric acid, dissolved in hot water" (p. 327). "XII. *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." (pp. 327–328). Presumably, aqueous solutions of DCPD and MCPM, respectively, were prepared; therefore, one can claim that MCPM and DCPD were differentiated by 1819. Furthermore, "XIII. *Subphosphate of Lime*. This salt occurs native under the names of apatite or asparagus stone" (p. 328). Since the prefix "sub-" means "incomplete," one can claim that a shortage of orthophosphate ions in apatites (if compared with phosphate of lime) was confirmed.

Various preparation processes of a pure calcium orthophosphate currently known as CDHA were developed by 1807 [38]: "Phosphate of Lime may be obtained quite pure either by ſaturating the pure acid with marble and then evaporating; or by waſhing bone-aſh with hot water to diſſolve out any ſoluble ſalt which it may contain; then adding a little acetous or dilute muriatic acid till the efferveſcence ceaſes to engage the carbonat of lime which it contains, and again thoroughly edulcorating. Phoſphat of lime is produced alſo by double decompoſition, on dropping a ſolution of any phoſphated alkali into any ſoluble calcareous ſolution that has not any great exceſs of acid. Vauquelin alſo found that on boiling phoſphat of ſoda with wet and newly precipitated carbonat of lime, the ſame reſult took place, and carbonate of ſoda with phoſphate of lime were produced." (p. 221). One can see that some of these processes are still used to produce chemically pure CDHA. In the fourth edition of *Encyclopædia Britannica* (1810), applications of calcium orthophosphates were described as follows [40]: "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." (p. 585). Although it is slightly beyond the subject, one should mention that calcium orthophosphite ($Ca_3(PO_3)_2$) with trivalent P was also mentioned in that edition of Encyclopædia Britannica, as "phoſphite of lime" (p. 586).

In 1819, the major properties of CDHA were described as follows [39]: "4. 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. 5. 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." (p. 327). Here, one can see the earliest mentioning of the terms "atom" and "atomic theory."

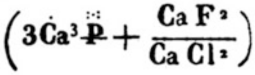
In 1823, W. Henry described the following compounds containing calcium and phosphorus [41]: *phosphuret of lime* obtained by passing phosphorus over red-hot lime (p. 565), which was, obviously, calcium phosphide (Ca_3P_2). It "has the remarkable property of decomposing water and the water afterwards contains phosphite, or hypophosphite, not phosphate of lime.* Drop a small piece of it into a wine-glass of water, and in a short time bubbles of phosphuretted hydrogen gas will be produced; which, rising to the surface, will take fire, and explode" (p. 566), followed by references to two publications written by the famous French chemist and physicist Joseph Louis Gay-Lussac (1778–1850), to whom this discovery was credited. Obviously, the "phosphuretted hydrogen gas" was a mixture of PH_3, P_2H_4, and more complicated PH compounds. Then, W. Henry described *phosphate of lime* [41], which "is constituted, according to Mr. Dalton's experiments, of 49 acid + 51 lime, proportions which authorize us to consider phosphate of lime as consisting of 1 atom of acid = 28, + 1 atom of base = 28, the compound atom being 56" (pp. 566–567). Here, the term "atom" was used again. In addition, this is an evidence that the famous English chemist, meteorologist, and physicist John Dalton (1766–1844), who is best known for his pioneering work in the development of modern atomic theory, as well as his research into color blindness (sometimes referred to as daltonism, in his honor), also contributed to calcium orthophosphates. Afterward, other calcium orthophosphates were mentioned as follows [41]: "*Bi-phosphate of lime* may be formed by digesting phosphate of lime with a quantity of phosphoric acid equivalent to that already engaged in the salt" (p. 567). Obviously, it was DCPD. "*Tri-phosphate of lime*. – This salt, according to Mr. Dalton, perhaps formed by adding pure phosphoric acid to lime water, until a commencement of precipitation appears, when a drop or two of acid must clear the solution. If the solution be evaporated to dryness at a moderate heat, and then dissolved in water again, simple phosphate of lime remains, and a quadri-phosphate exists in the solution." (p. 567). Unfortunately, this description does not allow to identify calcium orthophosphates. They might be DCPD (in solution) and DCPA (evaporated to dryness at a moderate heat) or OCP (in solution) and either ACP or CDHA (evaporated to dryness at a moderate heat): "*Quadri-phosphate of lime*. – If 100 parts of phosphate of lime be digested for 24 hours with 87 parts of sulphuric acid, diluted with a sufficient quantity of water, and be then filtered, the liquid which passes through contains the whole of the phosphoric acid, with only one-fourth of the lime which existed in the original salt ... The dissolved salt is therefore a compound of 1 atom of lime = 28 + 4 atoms of acid = 112. When evaporated it forms, on cooling, pearly scales, which have an acid taste, and dissolve readily in water, giving a solution of the sp. gr. 1,44." (p. 567). Obviously, this was MCPM with a possible admixture of MCPA formed after evaporation. Although the meaning of the statement "1 atom of lime = 28 + 4 atoms of acid = 112" remains unclear, one may guess that the numerical values 28 and 112 should be a kind of molar masses. Indeed, 28 is 50 % of the molar mass of CaO, i.e., this is a gram equivalent (synonym: an equivalent weight). According to Wikipedia, the equivalent weights were established by 1777 [42]; therefore, this suggestion sounds reasonable. Finally, W. Henry [41] mentioned "*Octo-phosphate of lime*. – Mr. Dalton is of opinion that a compound of 8 atoms of acid and 1 atom of lime is the true result of the process described under the last head; and that a compound of as many as 12 atoms of acid with one of lime may exist, forming a dodecaphosphate" (p. 567). Such superacidic calcium orthophosphates are currently unknown; moreover, they were excluded from the books published in 1828 [43] and 1829 [44]. Presumably, chemists quickly found a mistake. In addition, in the latter book, one can read the following [44]: "The *biphosphate of lime* may be prepared by adding one atom of phosphoric acid to one atom of the phosphate of lime" (p. 252). Here, the term "an atom" undoubtedly means either "a molecule" or "a mole," i.e., the correct chemical understanding of the stoichiometry of DCPD preparation from H_3PO_4 and TCP was achieved by 1829.

By 1827, the German mineralogist Gustav Rose (1798–1873) established the correct understanding of the chemical composition of apatites. To demonstrate this, let me cite a publication of 1859, coauthored by the famous French chemist Henri Étienne Sainte-Claire Deville (1818–1881) [45]: "The singular composition of apatite, first determined by M. Gustav Rose in 1827, shows that it is a definite compound of chloride and fluoride of calcium with phosphate of lime" (p. 128). In 1832, a chemical term "tribasic phosphate of lime" (p. 90), which fully corresponds to both α-TCP and β-TCP, was mentioned for the first time [46].

Coincidently, the famous German chemist Eilhard Mitscherlich (1794–1863), who was a learner and a friend of J.J. Berzelius and who today was best remembered for his law of isomorphism (1819), also worked in this area. To prove this, let me cite an introduction from a paper of 1833, written by the Scottish chemist Thomas Graham (1805–1869), clearly demonstrating the established knowledge on phosphates and arsenates by that time [47]: "No classes of salts have more liberally rewarded investigation than the arseniates and the phosphates. Witness the discovery of the extraordinary phosphates of lime by Berzelius; the observation of the identity of form of the corresponding arseniates and phosphates by Mitscherlich, and the doctrine of isomorphism to which that observation led; the discovery by the same chemist of two biphosphates of soda, agreeing in composition but differing in form; and lastly, the discovery of the pyrophosphates by my friend and townsman Mr. Clark. Much, however, still remains to be done to complete the history of these interesting salts." (p. 253). In addition, various modifications of phosphoric acid, currently known as orthophosphoric, pyrophosphoric, and metaphosphoric acids, were already known. On p. 281 of his paper, Graham called them as "a terphosphate, a biphosphate, and phosphate of water," respectively [47].

Concerning chemical formulae of calcium orthophosphates, the earliest ones were discovered in the aforementioned paper by Graham [47] as $\dot{\mathbf{C}}\mathbf{a}^{\mathbf{2}}\overset{\cdots}{\ddot{\mathbf{P}}}$ and $\dot{\mathbf{C}}\mathbf{a}^{\mathbf{3}}\overset{\cdots}{\ddot{\mathbf{P}}}$ (p. 265). Another type of the chemical formulae with struck out phosphorus was published in 1844 by Mitscherlich [48] as $2.Ca^2P$ and $5.Ca^2P$ (p. 69[a]). Furthermore, a combination of both styles with dots above the element's symbols as in Ref. [47]

and striking out phosphorus as in Ref. [48] (additionally, chlorine was written as Cl and fluorine was written as F) was also used [49]. Even such a complicated way of writing with dots, striking out and mathematical fractions as



$$\left(3\dot{C}a^{3}\overset{:\cdot:}{\cancel{P}}+\frac{Ca\,F^{2}}{Ca\,Cl^{2}}\right)$$

was used on page 399 of Ref. [50] to describe the chemical composition of apatite. One can see that initially neither hydrogen nor oxygen was included into the chemical formulae of calcium orthophosphates. Nevertheless, this topic kept developing. For example, the correct but just strange-looking chemical formula of apatite as $3Ca_3O_3,P_2O_5 + CaCl\ F$ might be found on page 29 of a book published in 1841 [51]. However, in another book of 1841 [52], the numerical subscripts were replaced by superscripts; therefore, the chemical formula for bone phosphate of lime was written as $8CaO + 3P^2O^5$, that for triphosphate of lime as $3CaO + P^2O^5$, that for diphosphate of lime as $2CaO + P^2O^5 + 1$ eq. basic water, and one for phosphate of lime as $CaO + P^2O^5 + 2$ eq. basic water (p. 304). Obviously, the term “basic water” means acidic orthophosphates; therefore, these formulae were the first correct ones for CDHA, TCP, DCPD/DCPA, and MCPM/MCPA, respectively (hydrate water was not mentioned yet). Similar way of writing was used in some later books, such as a publication of 1854 [53], in which the chemical formula of “calcis triphosphas. – triphosphate of lime.” was written as $3CaO,PO^5$ (p. 625) and the chemical formulae of other calcium orthophosphates were written as $2CaO,PO^5$ (p. 626) and $8CaO,3PO^5$ (p. 627), as well as a publication of 1859 [45]: “Apatite has the composition $3(PO^5, 3CaO)\{^{Cl}{}_{F}\}Ca$” (p. 128). In the latter formula, anions were placed ahead of cations. In addition, in 1843 and 1845, John Percy published identical papers [54, 55] (the earliest example of redundant publications?), in which he described formation of “a new hydrated phosphate of lime” with a chemical formula $2CaO + PO_5 + 6HO$, with “1 equiv. water being basic and 5 constitutional.” Obviously, the “basic water” means existence of $HPO_4{}^{-}$, which is typical for DCPD, OCP, and CDHA, while the “constitutional water” is the hydrate water. Since only OCP contains a combination of $HPO_4{}^{-}$ with 5 molecules of hydrate water (Table 15.1), presumably, John Percy prepared OCP.

With a few exceptions [47, 54, 55], the aforementioned information on apatites and other calcium orthophosphates was taken from various books. In addition, a limited amount of journal publications of the first half of the nineteenth century is also available. Namely, research papers on the subject were published by the famous Swedish chemist Jöns Jacob Berzelius (1779–1848) [56, 57], as well as by G.O. Rees [58], M. Baruel [59], the English physician and chemist Henry Bence Jones (1813–1873) [60–62], J.D. Smith [63], and J.L. Lassaigne [64]. Among them, a paper of 1845 by Jones [60] should be noted. Namely, let me cite a figure caption: “Amorphous deposit in alkaline urine. Deposit on boiling phosphate of soda with chloride of calcium, or with sulphate of magnesia” (p. 349). This statement is astonishing because it might be considered as the earliest mentioning on ACP [65], 50 years before discovering X-rays in 1895 by the famous German scientist Wilhelm Conrad Röntgen (1845–1923)! Furthermore, Jones published the earliest-found pictures of precipitated crystals and some of them belonged to calcium orthophosphates (Fig. 15.1). Next early pictures of calcium orthophosphate precipitates from urine might be found in publications of 1859 [66] and 1860 [67].

In the end of the 1840s, the earliest-found solubility experiments of calcium orthophosphates were performed by Lassaigne [64]. Those experiments were carried out in water, saturated with carbon dioxide. The following data were obtained by 1847: "1. *Pure phosphate of lime*, obtained by the double decomposition of a calcareous salt and alkaline phosphate; the solubility was 0·000750. 2. *Fresh* bone, a piece of nearly two inches long, 46/100 dths of an inch wide, and 4/100 dths thick; solubility 0·000166. 3. Bone disinterred after about twenty years' repose in a cemetery, the subsoil of which was sandy; solubility 0·000300." [64]. One can see that the solubility value of pure phosphate of lime (presumably, it was either precipitated ACP or CDHA) was found to be higher than those of bones. In 1849, it was stated 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." [68]. Thus, a higher solubility of both calcium orthophosphates and calcium carbonate in very weak acids was a well-known fact. The solubility data were updated in a publication of 1855 [69]: "Apatite dissolves in 393,000 parts of water saturated with carbonic acid; Artificial neutral phosphate, freshly precipitated, in 1,503 parts; Artificial basic phosphate, freshly precipitated, in 1,102 parts" (p. 27). Furthermore, "apatite requires 356 times as much liquid for its solution, as the same salt artificially prepared" (p. 28). Obviously, the "artificial basic phosphate, freshly precipitated," was ACP, and, indeed, the differences in solubility values between ACP and the stoichiometric well-crystallized HA might be that big. The results of the successive solubility experiments were published in 1866 [70], 1868 [71], 1871 [72, 73], and 1883 [74].

The second half of the nineteenth century started with "Chemistry" by Wilson, published in 1850 [75]. 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, $3CaO,PO_5$." (p. 219). Thus, various types of calcium orthophosphates were known already. 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" (p. 164). Thus, the compositional differences between the chemical formulae of the oxygen-containing calcium

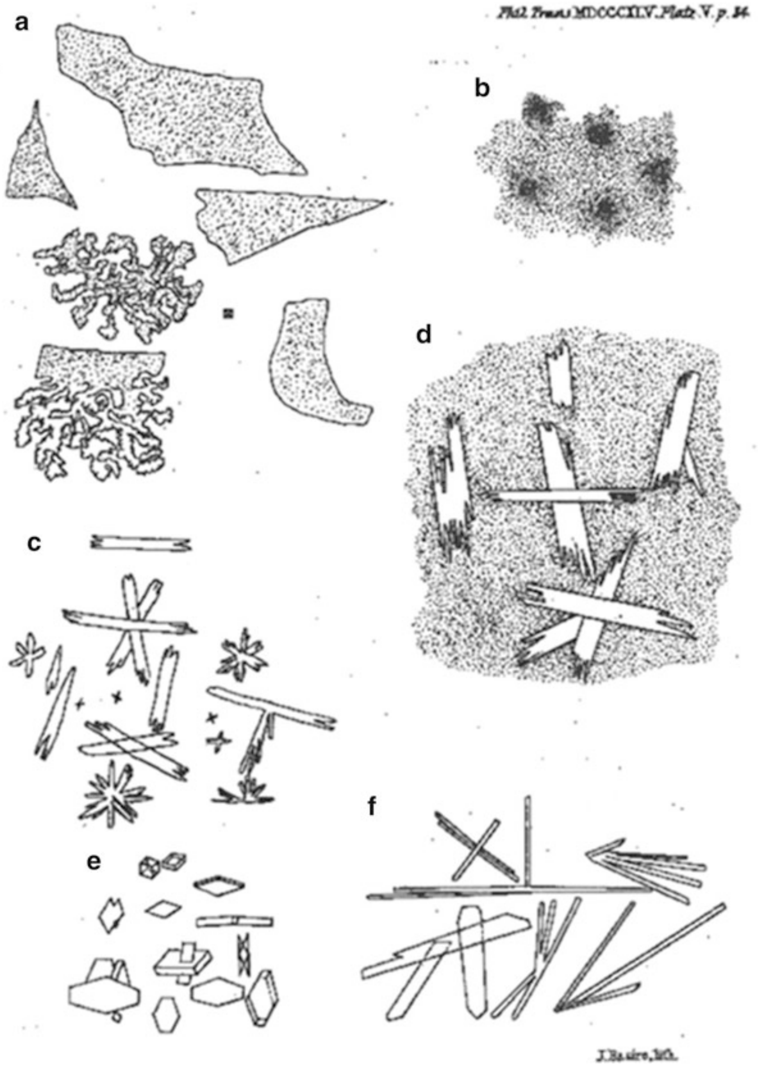


Fig. 15.1 The earliest available pictures of precipitates, some of which contain calcium orthophosphates "(**a**) Iridescent pellicles on some alkaline urine; (**b**) Amorphous deposit in alkaline urine. Deposit on boiling phosphate of soda with chloride of calcium, or with sulphate of magnesia; (**c**) Chloride of calcium with acid phosphate of soda, or with common phosphate of soda, after long standing; (**d**) Phosphate of soda with little chloride of calcium. Bone-earth phosphate; (**e**) On boiling phosphate of soda with sulphate of magnesia and little biphosphate of soda; (**f**) Phosphate of soda with sulphate of magnesia; after long standing" (p. 349). Namely, the precipitates on (**b**) are ACP (in the case, calcium chloride was used) and the crystals on (**c**) and (**d**) are either DCPD or OCP (Reprinted from Ref. [60])

phosphates and the oxygen-free calcium phosphides were clearly established by 1850. The earliest-found thesis on calcium orthophosphates was defended in 1853 [76]. In a publication of 1859, various preparation techniques of apatites were described as follows [45]: "M. Daubrée has prepared apatite by passing chloride of phosphorus over lime; M. Mauross and M. Briegleb, in continuation of the remarkable researchers made in the laboratory of Professor Wöhler, have reproduced apatite in more distinct and more beautiful forms by taking advantage of the double decomposition of alkaline phosphates and chloride of calcium; M. Forchhammer, by acting on phosphate of lime with chloride of sodium, has obtained very beautiful specimens of the same mineral species." (pp. 129–130). Here, the readers' attention was also paid to the names of additional early contributors to calcium orthophosphates.

In "Chemistry" by Brande and Taylor, published in 1863 [77], one can find the following statements: "Common Phosphate of Lime; Tribasic Phosphate of Lime; Bone Phosphate; $(3(CaO),PO_5)$. This salt occurs abundantly in bone-ash, and is found as a mineral product" (p. 331). 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" (p. 332). 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" (p. 331). This seems to be the second earliest mentioning on ACP. 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 lime" (p. 332), means that by 1863, researchers were aware of this fact.

Further historical description is based on the journal publications only. Namely, C. Morfit [78]; 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 [70, 72, 79, 80]; and R. Fresenius [81] also worked with calcium orthophosphates. Interestingly, C. Morfit wrote the chemical symbol of phosphorus as Ph, and, thus, he wrote the chemical formula of tribasic phosphate as $3CaO, PhO_5$ [78]. Furthermore, let me cite a paragraph from a Warington's paper of 1866 [70]: "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." (pp. 296–297). Thus, TCP, DCP, and OCP have been differentiated from each other by 1866, while, in fact, at least, 20 years earlier because Berzelius died in 1848. Furthermore, the researchers were already aware of 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 [70, 72, 79, 80], Ref. [70] by Robert Warington Jr. deserves both a special attention and extensive citations. For example, to prove that OCP indeed was already known by 1866, let me make another citation from Ref. [70]: "Octocalcic phosphate can only be produced by the simultaneous formation of monosodic phosphate:

$$8\mathrm{CaCl_2} + 5\mathrm{Na_4H_2P_2O_8} = \mathrm{Ca_8H_2P_6O_{24}} + 16\mathrm{NaCl} + 2\mathrm{Na_2H_4P_2O_8}.\text{''}\quad (\text{p. } 300)\,.$$

One can see a balanced chemical equation, 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 primitive chemical formulae without oxygen, such as $2.\mathrm{Ca}^2\mathrm{P}$ and $5.\mathrm{Ca}^2\mathrm{P}$ [48], 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 $\mathrm{Ca_2H_2P_2O_8{\cdot}4H_2O}$, demands 26·16 per cent. of water" (p. 299). Needless to explain, "$\mathrm{Ca_2H_2P_2O_8{\cdot}4H_2O}$" represents two molecules of DCPD (see Table 15.1). Furthermore, "It is interesting to observe that while disodic phosphate is of an alkaline nature, dicalcic phosphate possesses faint acid properties" (p. 300). 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." (pp. 300–301). 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:

$$4\mathrm{Ca_2H_2P_2O_8} + 6\mathrm{NH_3} = \mathrm{Ca_8H_2P_6O_{24}} + 6\mathrm{NH_4.P_2O_8}.\text{''}\quad (\text{pp. } 301-302)\,.$$

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" (p. 304) has two important consequences: (1) by 1866, this fact was not quite clear yet; (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.

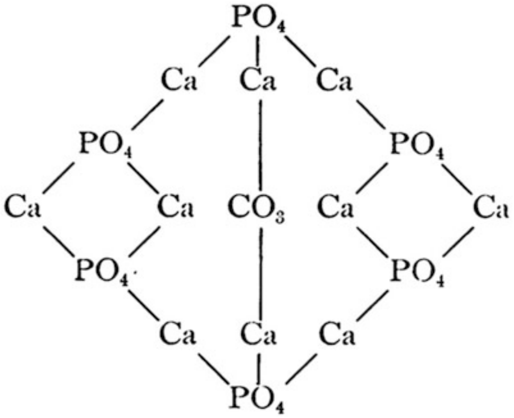


Fig. 15.2 The first available structure of a bone mineral, currently known as carbonate apatite (Reprinted from Ref. [83])

The latest available publication by Warington of 1873 [80] 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 $3Ca_3P_2O_8$. $CaOH_2O$ (i.e., HA – see Table 15.1) 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" (p. 989). 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 [82].

Now it would be logical to cite a publication of 1906 by Wells [83]: "The apparent constancy of the proportion of carbonate and phosphate of calcium in bones made 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" (p. 522) – see Fig. 15.2. 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" (p. 523). Obviously, the atomic arrangement shown in Fig. 15.2 represents the earliest structural drawing of a single molecule of an ion-substituted calcium orthophosphate, currently known as carbonate apatite. An attentive reader will notice two different types of calcium (currently known as Ca(1) and Ca(2)) in that structure. Besides, that time, apatites were considered as combined compounds, which results from this citation of 1879 [84]: "Calcium phosphate, combined with calcium chloride or calcium fluoride, occurs in the well-known minerals, apatite and osteolite" (p. 188). One might guess that, in the nineteenth century, the atomic arrangement of single molecule of carbonate apatite

(Fig. 15.2) could have inspired researchers to compose similar drawings for the single molecules of FA, HA, and/or chlorapatite; unfortunately, I have succeeded to find nothing 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 [31], in 1863, were written using chemical equations [77]: "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:

$$3\,(\mathrm{CaO})\,,\mathrm{PO_5} + 3\mathrm{SO_3} = 3\,[\mathrm{CaO}, \mathrm{SO_3}] + \mathrm{PO_5}.\text{"}\quad (\text{p.}\ 331)\,.$$

One can see that hydrogen was not included into the chemical formulae yet. Nevertheless, already in 1866, it was included by Robert Warington Jr. [70] (see above). Furthermore, chemical formulae of various types of phosphates (namely, metaphosphate and acid phosphate), as well as differences in their solubility, were known by 1881 [24]: "In order to prepare phosphorus, the bone-ash is first mixed with so much dilute sulphuric acid as to form the acid phosphate:

$$\mathrm{Ca_3(PO_4)_2} + 2\mathrm{H_2SO_4} = \mathrm{CaH_4(PO_4)_2} + 2\mathrm{CaSO_4}.$$

The solution of this soluble acid phosphate is next poured off from the precipitated gypsum, and evaporated to dryness, after which, the solid residue heated to redness, water is given off and calcium metaphosphate formed:

$$\mathrm{CaH_4(PO_4)_2} = \mathrm{Ca(PO_3)_2} + 2\mathrm{H_2O}.$$

This salt is then carefully mixed with charcoal, and heated to bright redness in earthenware retorts shown in Fig. 15.2, when the following change takes place:–

$$\mathrm{Ca(PO_3)_2} + 10\mathrm{C} = \mathrm{P_4} + \mathrm{Ca_3(PO_4)_2} + 10\mathrm{CO}.\text{"}\quad (\text{p.}\ 460)\,.$$

Now, it is time to describe miscellaneous studies on the subject. The first accessible journal paper on detection and preservation techniques of various deposits, including calcium orthophosphates, was published in 1852 [85]. Presence of calcium orthophosphates in teakwood was established in 1862 [86]. Neutral phosphates of lime were further investigated in 1872 [87]. Various analytical topics on calcium orthophosphate chemistry have been studied since, at least, 1863 [88] and remained to be a subject of active research approximately until the 1910s [89–102]. The quantitative analysis of a calcium orthophosphate was performed in 1884 [103], followed by remarks by C. Glaser in 1885 [104]. In the 1880s, occurrence of apatite [105] and TTCP [106–108] in metallurgical slags was discovered. The latter discovery belongs to the German metallurgist Gustav Hilgenstock (1844–1913), after whom TTCP is called hilgenstockite. An attempt of a direct estimation of phosphoric acid as the tribasic phosphate of lime was performed in 1888 [109]. A chemical interaction of TCP with carbon dioxide and iron hydroxide was investigated in 1891 [110].

Besides, in the second half of the nineteenth century, calcium orthophosphates were extensively investigated as fertilizers. As written above, the term "superphosphate" has been known since 1795 [34] and was further developed in 1803 [111]: "The phoſphoric acid ſeparated from that portion of lime, immediately combines with the reſt of the phoſsphate of lime, and forms ſuper phoſphate of lime, which is not farther decompoſable by ſulphuric acid" (pp. 394–395). Obviously, initially it represented just acidic calcium orthophosphates. However, by the second half of the nineteenth century, a fertilizer with the same name became popular. It consisted of "a mixture of the last-mentioned compound and sulphate of lime" [84]. According to Pusey [112], this finding belongs to the famous German chemist Justus Freiherr von Liebig (1803–1873), who is considered as "the father of the fertilizer industry" for his discoveries. Let me cite Pusey [112]: "Dr. Liebig's great discovery of dissolving bones in sulphuric acid for the purpose of manure, has been so clearly established by the experiments as well of the Duke of Richmond as of other farmers, and so fully investigated by Mr. Hannam, that nothing seems now to be wanted but some plan for bringing it within the ordinary routine of farming." (p. 324). In a publication of 1864 [113], one can read the following: "Now, superphosphate of lime is composed, necessarily, of soluble phosphate of lime and plaster, or sulphate of lime formed from a combination of the sulphuric acid employed in the manufacture of superphosphate with the lime of the bones" (p. lv). More than 20 research papers on superphosphate were published by the beginning of the twentieth century, which indicated to the importance of this chemical for the human being [114–136]. One can see that almost all of these studies were performed and published by single researchers (see individual comments to Refs. [115, 121]), while the majority of the investigations were devoted to analytical chemistry.

Although vitrification properties of some forms of calcium orthophosphates upon heating have been known since, at least, 1804 [33], the first accessible journal paper on this topic was published in 1877 [137]. The modern chemical formula of perfectly transparent crystals of natural FA as $Ca_5(PO_4)_3$ F has been known since, at least, 1873 [138], while chemical formulae of DCP (as "mono-hydrogen calcium orthophosphate, $HCaPO_4$") and MCP (as "tetra-hydrogen calcium phosphate, $H_4Ca(PO_4)_2$") [84] have been known since, at least, 1879 (pp. 205–206). Interestingly, in a publication of 1871, the chemical formulae of calcium orthophosphates were written in different ways: as 3CaO PO_5 for apatite and CaO 2HO PO_5 for "some acid phosphate of lime" [73]. Thus, by the 1880s, the rules on how to write chemical formulae of inorganic compounds have not been standardized yet.

Additionally, one should briefly mention the earliest biochemical applications of calcium orthophosphates. Let me cite a couple of self-explanatory sentences from a publication of 1935 [139]: "Calcium phosphate was used for enzyme separation as early as 1860 by Brücke (cited by Effront, 1917). Its use for precipitation of active immunological material was advocated for the purification of diphtheria toxin first by Roux and Yersin in 1889, ..." (p. 150). Thus, the famous French physician, bacteriologist, and immunologist Pierre Paul Émile Roux (1853–1933) and the famous Swiss and French physician and bacteriologist Alexandre Emile Jean Yersin (1863–1943) also contributed to calcium orthophosphates by performing absorption and purification of diphtherial toxin.

Finally, one should report the investigations performed by the British clinician and pharmacologist Sydney Ringer (1836–1910), whose name is remembered in a Ringer's solution. It is an aqueous isotonic solution of several inorganic salts mimicking the body fluids of animals [140]. Within 1882–1885, Ringer determined that a solution perfusing a frog's heart must contain several inorganic salts in a definite proportion if the heart was to be kept beating for long [141–145]. The following citation from his works is worth mentioning [143]: "*(g)* So that we find we possess an excellent circulating fluid capable of maintaining the heart for several hours, which consists of phosphate of calcium saline, with potassium chloride" (p. 19).

To conclude the 1800s, one should recognize that the majority of the fundamental discoveries in chemistry of calcium orthophosphates were made in the nineteenth century.

15.4.3 From 1900 till 1950

As the modern scientific databases comprise of scientific papers published after 1900, the history of calcium orthophosphates in the twentieth century is based on the journal publications only. This approach allows establishing the real chronological order. However, the detailed description of every publication on the subject becomes impossible due to permanently increasing amount of them.

The twentieth century started with the systematic studies performed by F.K. Cameron with co-workers [136, 146–153] and H. Bassett [154–157]. Namely, in 1908, Bassett composed the first version of the solubility diagram $CaO–P_2O_5–H_2O$ (Fig. 15.3) [156]. According to the literature [24, 84, 158], by that time, researchers already worked with the individual calcium orthophosphates; however, not all the chemical formulae appeared in close resemblance to the ones we use today. For example, H. Bassett wrote formulae of MCPM and MCPA as $CaH_4P_2O_8.H_2O$ and $CaH_4P_2O_8$, respectively. In addition, he mentioned hydrated forms for TCP and TTCP as $Ca_3P_2O_8.H_2O$ and $Ca_4P_2O_9.H_2O$, respectively [156], which are currently unknown. A study on dissolution kinetics of several calcium orthophosphates was published in 1910 [159]. Binary salts of calcium orthophosphates with orthophosphates of other chemical elements have been known since, at least, 1911 [160]. The osmotic properties of calcium orthophosphates were investigated in 1915 [161]. 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 [162], while a neutralization reaction of H_3PO_4 by $Ca(OH)_2$ was investigated in 1923 [163]. Preparation of

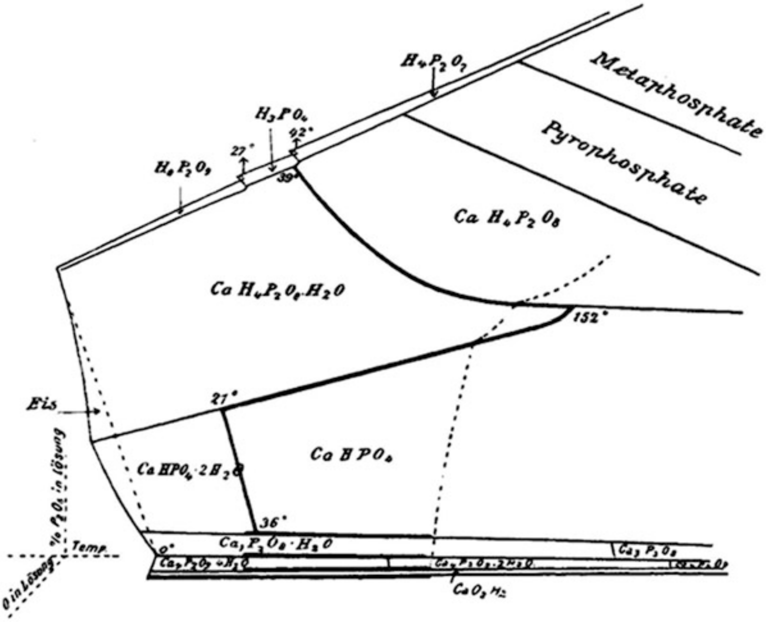


Fig. 15.3 The system CaO–P_2O_5–H_2O in 1908 (Reprinted from Ref. [156]). In 1917, Ramsay published important information on calcium orthophosphates [169]: "1. The substances sold as "Phosphate of lime" and "Calcium Phosphas B.P." are not pure tricalcic phosphate but are mixtures of di- and tricalcic phosphates. 2. Sodium phosphate (Na_2HPO_4) added to ammoniacal calcium chloride and the resulting precipitate washed with water yields a mixture of di- and tricalcic phosphate and calcium hydrate. 3. Bone ash dissolved in hydrochloric acid and precipitated with ammonia, the precipitate being well washed, yields also a mixture of di- and tricalcium phosphate and calcium hydrate. 4. When three equivalents of lime (3CaO) are made to act on one equivalent of phosphoric acid (P_2O_5) and the resulting precipitate removed with little delay pure tricalcium phosphate is obtained." Obviously, the obtained "mixture of di- and tricalcium phosphate and calcium hydrate" was a CDHA; therefore, a nonstoichiometric nature of the precipitates was established by 1917. Furthermore, one can see that chemically pure calcium orthophosphates (B.P. means British Pharmacopoeia) were commercially produced by 1917

calcium orthophosphate (presumably, it was ACP) in a colloid state was reported in 1921 [164]. An interesting note on "liquid crystals of calcium phosphate" was published in 1922 [165]; in fact, the author prepared MCPM. The first paper on in vitro mineralization using aqueous solutions containing ions of calcium and orthophosphate was published in 1926 [166], followed by publications of 1932 [167] and 1933 [168]. These studies might be considered as predecessors of current mineralization investigations using simulating body fluid (SBF) and other artificial simulating solutions.

Furthermore, by 1928, it was clearly known that TCP could not be prepared by wet precipitation [170]: "*We have been unable to find any evidence of the existence of a molecular species with the formula $Ca_3(PO_4)_2$*. 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 $Ca_3(PO_4)_2$. No one has succeeded in preparing it by precipitation [12, 35–48], bearing out the theoretical objections to such a reaction on the grounds that fifth order reactions do not occur [49]. 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." (p. 128). Other researchers [171] made similar conclusions. Nevertheless, that time 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" [172]. This controversy was explained in 1940 by a matter of definitions [173]: "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 P_2O_5:CaO ratios approaching that of $Ca_3(PO_4)_2$." (p. 265). Nevertheless, papers on precipitated TCP [174, 175] and even on precipitated TCP hydrate [176] kept publishing even in the 1940s. An interesting distinction between HA and precipitated TCP hydrate (obviously, it was CDHA with $x = 1$; see Table 15.1) was made in a latter paper [176]: "It seems safe to conclude that a precipitated tricalcium phosphate can be designated as a hydroxyapatite when a 1-gram charge of 900 ºC. calcine registers a dissolubility of less than 20 % by a continuously agitated 1-hour digestion in the ammonium citrate reagent at 65 ºC. In contradistinction, a tertiary precipitate is identified as a tricalcium phosphate hydrate when a like charge of its calcine shows dissolubility of as much as 50 % by the stipulated citrate digestion." (p. 169). Currently, we are able to explain the solubility differences between these two calcined samples by formation of more soluble β-TCP (Table 15.1).

The crystal structure of apatites was established in 1930 [177, 178], followed by a great study on the structural characteristics of apatite-like calcium orthophosphates of various origins in 1931 [179]. Such terms as hydroxyfluorapatite, $Ca_{10}(F,OH)_2(PO_4)_6$, OA, and carbonate apatite were already known. Besides, the aforementioned "hydrate of tricalcium phosphate, $Ca_9(H_2O)_2(PO_4)_6$," with the molecular weight of 966.4 g and apatite-like diffraction pattern was mentioned as well [179]. The "apatite-like diffraction pattern" clearly indicates that the authors prepared CDHA. The structures of carbonate apatite [180, 181] and DCPD [182] were reported in 1937 and 1938. Furthermore, in 1938, several calcium orthophosphates were X-ray studied to determine their variability and phase purity [183]. The following citation from the abstract is rather interesting: "The commercial tertiary calcium phosphates are probably hydroxylapatite with more or less adsorbed phosphate ions resulting in empirical formulas approaching the theoretical value for $Ca_3P_2O_8$. Secondary calcium phosphate may be admixed" (p. 156). Interestingly, in 1938, the structure of TCP was sometimes considered as that of HA with adsorbed PO_4 ions (presumably, with the counterions) on the surface; still, the chemical formulae were expressed differently to the ones we know today. The detailed investigations on isomorphic substitutions in apatites have been performed since 1938 [184].

In the second quarter of the twentieth century, solubility of apatites and other calcium orthophosphates was investigated extensively. Namely, papers on this topic were published in 1925 [185–187], 1926 [188], 1927 [189–191], 1929 [152], 1931 [192, 193], 1937–1939 [194–197], 1942 [198, 199], 1945 [200, 201], 1948 [202–204], and 1950 [205]. In addition, in 1949, a paperback monograph (or thesis?) on enamel-apatite solubility was published [206]. Buffering abilities of the dissolved calcium orthophosphates have been known since, at least, 1933 [207]. Additionally, in 1931–1933, Bredig et al. [208], Trömel [209], and Schneiderhöhn (a reference was not found) differentiated α- and β-modifications of TCP (see Table 15.1) and created the initial versions of the high-temperature diagram for the binary system $CaO–P_2O_5$. In 1933, reduction experiments of TCP by carbon, carbon monoxide, and hydrogen were performed at temperatures of 900–1,300 °C [210]. In addition, a new set of extensive studies on superphosphate was initiated in the 1930s [211–219] and continued ever since (more recent references are not cited due to their abundance). Besides, in 1934, an important (for fertilizers) reaction between urea and several calcium orthophosphates was investigated [220]. In 1935, the heat capacity values of calcium orthophosphates were measured [221]. Very popular at the turn of this millennium silicon- (or silica-) contained calcium orthophosphates, in fact, appear to have been known since, at least, 1937 [222–224], simultaneously with defluorination studies of natural phosphate rocks [224–226]. Applications of calcium orthophosphates for removal of fluorides from water have been known since, at least, 1938 [227–229], while the earliest research paper on using calcium orthophosphates in chromatography was published in 1942 [230].

In 1940, a fundamental study on the equilibrium in the system $CaO–P_2O_5–H_2O$ was published [231]. Besides, in 1940, the available level of knowledge on basic calcium orthophosphates (TCP, TTCP, and apatites) was summarized into a big review [173], which might be considered as the first comprehensive review on the subject. That time, the existence of OA was uncertain. In addition, the authors of that review wrote about HA that "Existence as a unique stoichiometric compound doubtful" (p. 259, Table 15.1), which was a clear indication to the great difficulties to synthesize HA but not CDHA. Furthermore, the following important assumption was made: "First, between dicalcium phosphate and lime, there exists, in the ternary system, a continuous series of solid solutions having an apatite lattice. It follows from this that tricalcium phosphate and hydroxyapatite do not exist in aqueous systems as unique, stoichiometric compounds" (p. 265). Thus, in 1940, existence of CDHA with variable Ca/P ratio was predicted. The idea on a continuous series of solid solutions was further developed by 1950 [232]: "On structural grounds it appears possible that a continuous series of apatite-like solid solutions can exist between octocalcium phosphate and hydroxy- (or fluor-) apatite. In practice, no two preparations with composition lying between octocalcium phosphate and hydroxyapatite are likely to be identical" (Abstract). Thus, in 1950, the distinct Ca/P borders for CDHA were established between those in OCP (Ca/P = 1.33) and HA (Ca/P = 1.67). In addition, it was noted that calcium orthophosphate precipitates with Ca/P ratios within 1.0–1.33 “consist of at least two phases; dicalcium phosphate and a solid at least as basic as octocalcium phosphate” (Abstract) [232].

The term “whitlockite” (named after an American mineralogist Herbert Percy Whitlock (1868–1948), who was the curator of the American Museum of Natural History, New York, USA) for ion-substituted TCP first appeared in 1941 [233]. Also, in the same year, a study on virus purification by adsorption on calcium orthophosphate was published [234], followed by two other studies in 1945 [235, 236]. An important study on the thermal decomposition of MCPM was published in 1947 [237], while that on high-temperature heat content of HA appeared in 1950 [238].

To finalize the first half of the twentieth century, one should mention on an interesting conclusion, made in 1944. Namely, attempting to explain anomalous pH drop during titration of H_3PO_4 by $Ca(OH)_2$ discovered by earlier researchers [163], Greenwald published a paper on a possibility to precipitate calcium orthophosphates having Ca/P ratio ≥2 [239]: “We may now picture the course of events as follows: after the first equivalent of calcium hydroxide has been added, the solution contains Ca^{++}, $H_2PO_4^-$ and $HPO_4^=$ ions. It also contains some undissociated $CaHPO_4$. This may act as an acid and upon addition of $Ca(OH)_2$ give a precipitate of $Ca(OH){\cdot}CaPO_4$, possibly occluding or adsorbing a little $Ca(OH)_2$ as well.” (p. 1306). In fact, precipitation of $Ca(OH){\cdot}CaPO_4$ remained unproven because there is no explanation as to why undissociated $CaHPO_4$ should behave as a stronger acid if compared with $H_2PO_4^-$ ions. Currently, we can explain that anomalous pH drop by formation of ACP, the chemical composition of which may vary in wide ranges (Table 15.1). A similar unproven conclusion on a possibility to precipitate calcium orthophosphates having Ca/P ratio exceeding that in HA due to adsorption of hydroxyl or other anions was published in 1950 [232].

More recent (after 1950) publications on calcium orthophosphates are not considered, since they are well known.

15.5 Calcium Orthophosphates as Bone Grafts

15.5.1 Artificial Grafts in the Nineteenth Century and Before

The artificial generation of tissues, organs, or even entire living organisms has been a matter of myths and dreams throughout the history of humankind. 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 nonbiological materials into the human body was noted far back in prehistory. Namely, according to Ratner [240]: “The remains of a human found near Kennewick, Washington, USA (often referred

Fig. 15.4 A wooden prosthesis of a hallux of a mummy (Reprinted with permission from Ref. [241]. Copyright 2001, American Chemical Society)

to as the "Kennewick Man") was dated to be up to 9000 years old. That 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. Another example of the introduction of foreign materials into the skin, dated to over 5000 years ago, is the tattoo. The carbon particles and other substances probably elicited a classic foreign-body reaction." (p. xli).

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 an $\sim$3,000-year-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-year-old woman whose toe was amputated (Fig. 15.4) [241]. Besides, the famous painting by Fra Angelico (ca. 1395–1455) "The Healing of Justinian by Saint Cosmas and Saint Damian" (Fig. 15.5), a visualization of the legend of twins Sts. Cosmas and Damien (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.

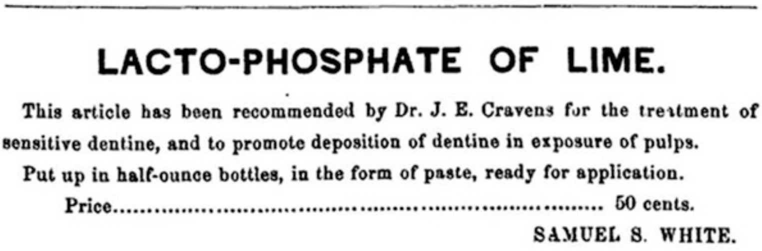
Fig. 15.5 Fra Angelico's (ca. 1395–1455) "The Healing of Justinian by Saint Cosmas and Saint Damian" (approximately 1439) is exhibited at Museo di San Marco, Florence, Italy

Historically, a selection of the materials was based on their availability and an ingenuity of the individual making and applying the prosthetic [242]. 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. 15.4), as well as some metals (gold or silver). For instance, "the father of Western medicine" Hippocrates (ca. 460 BC–ca. 370 BC) apparently used gold wire and linen thread for ligatures in the repair of bone fractures. Aulus Cornelius Celsus (ca. 25 BC–ca. 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 [243]. 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 [244]. Besides, while excavating Mayan burial sites in Honduras in 1931, archaeologists 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 [245]. This might 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. That implant was also described as properly bone integrated [246].

In the middle ages, one of the first scientific descriptions of congenital and acquired defects of the maxilla and their treatments was given by the famous French barber surgeon Ambroise Paré (ca. 1510–1590), who is considered as one of the "fathers of surgery and modern forensic pathology." In 1564, he published *Dix livres de la chirurgie, avec le magasin des instrumens necessaires à icelle*, where he specifically described defects of the palate with bone destruction caused by harquebus 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 1668, a book by the Dutch surgeon Job Janszoon van Meekeren (1611–1666) was published [247]. One of the most interesting works, performed by van Meekeren, was a reconstruction of the face of Duke Butterlijn, who received a piece of dog's skull bone to heal his skull defect that was caused by a Tartar sword. The duke recovered well but was banned by Russian priests, who considered that a combination of a Christian head with a dog bone was unacceptable for the church. Therefore, although the graft was completely healed, the duke asked the surgeon to remove it again [247].

In the eighteenth century, the first well-documented studies on autografts and allografts were published. Namely, the first journal paper on clinical use of a bone autograft belongs to the German surgeon and ophthalmologist Philipp Franz von Walther (1782–1849), who replaced surgically removed parts of a skull after trepanation [248], while the first journal paper on clinical use of a bone allograft belongs to the Scottish surgeon Sir William Macewen (1848–1924), who successfully reconstructed an infected humerus of a 4-year-old boy by a graft obtained from the tibia of a child with rickets [249]. Additional historical details on bone grafts are available in literature [250].

Concerning dentistry, at an early stage, a common method to replace teeth was the homologous transplantation of teeth in humans. Namely, the Scottish surgeon John Hunter (1728–1793) not only investigated in his pioneering work the effect of transplantation 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 [251]. Besides, various restorative materials might be used for feeling defects and capping exposed pulps and dental cavities. Currently they



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.

Fig. 15.6 An advertisement of the S.S. White company for “Lacto-Phosphate of Lime” 1873 (Reprinted from Dent. Cosmos 1873, 15, 683)

include zinc orthophosphate, zinc polyacrylate (polycarboxylate), amalgams, glass ionomer cements, calcium hydroxide, etc. [252, 253]; however, within the scope of this review, calcium orthophosphate-based formulations are considered only. According to the available literature, Dr. Junius E. Cravens (1844–1920) from the USA 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 [254]. This pulp-capping agent was brought to the market by the S.S. White company with the trade name “Lacto-Phosphate of Lime” (Fig. 15.6). Sugar-containing formulations were known as well [255]. To the best of my findings, that study by Cravens might be considered as the first mentioning on artificial calcium orthophosphate-based biocomposites and hybrid biomaterials (reviewed in Ref. [256]). Thus, one might claim that the grafting history of calcium orthophosphates started in the 1870s.

However, 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 to the body’s immunologically competent cells. Therefore, the use of implantable biomaterials did not become practical until the advent of an aseptic surgical technique developed by the British surgeon Sir Joseph Lister (1827–1912) in the 1860s. In addition, there was a lack of knowledge about a toxicity of the selected materials. Since the major inorganic components of the normal calcified tissues of mammals were established by 1808 [257], application of calcium orthophosphates and other calcium-containing compounds as artificial bone grafts became logical.

Historically, plaster of Paris (calcium sulfate) was the first widely tested artificial bioceramics. For example, according to Wikipedia, 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 nineteenth century, surgeons already used plaster of Paris as a bone-filling substitute [258]. Nevertheless, it was the 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 3 weeks later [259]. 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 [260, 261]. After the abovementioned case of lacto-phosphate of lime (Fig. 15.6), this seems to be the second well-documented grafting application of calcium orthophosphates.

To conclude this part, one should stress that the performance of living tissues is the result of millions of years of evolution, while the performance of acceptable artificial substitutions those humankind has designed to repair damaged tissues is 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 other publications [10, 12–15, 250, 262–265].

15.5.2 The Twentieth Century

According to the previous section, the initial attempts to use calcium orthophosphates for grafting purposes were performed in the end of the nineteenth century. However, in the aforementioned cases, either the biomedical applications of biologically produced calcium orthophosphates (Gluck) or dental applications not requiring any surgery (Cravens) were described. According to both the electronic databases and previous reviews on the subject [10, 12–15, 250, 262–265], 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 1920 [11] by the US surgeon Fred Houdlette Albee (1876–1945), who invented bone grafting [266] and some other advances in orthopedic surgery. The researchers injected either 0.5 or 1 c.c. 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 [11]. 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 to 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 hemi-arthroplasty for fracture [267]. In 1931, Murray also reported an acceleration of healing following implantation of calcium salts composed of 85 % TCP and 15 % $CaCO_3$ in canine long-bone defects [268, 269].

At the beginning of the 1930s, the classic osteoinductive phenomenon was defined well by Huggins [270], 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 [271, 272].

Simultaneously, in the 1930s, Haldeman and Moore [273], Stewart [274], Key [275], and Shands [276] discovered the fact that only certain types of calcium orthophosphates mentioned in Table 15.1 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 0.5–1.0 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 on delayed healing compared to control, while the presence of TCP at the site of the fracture appeared to favor the union [273]. Furthermore, Key [275] 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." (p. 176). 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" (p. 184). Stewart [274] 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" (p. 871). Shands [276] also reported conflicting effects of several calcium salts (calcium glycerophosphate, a mixture of TCP (3 parts) and $CaCO_3$ (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 [277]. Similar conclusions were obtained in 1951 by Ray and Ward [278].

Due to the reasons mentioned in the abstract, the historical events of the second half of the twentieth century are reported very briefly. Namely, in 1945, the first publication on applications of calcium orthophosphates as dentifrices was published [279]. Two important calcium orthophosphate-containing simulating solutions, namely, Earle's balanced salt solution (EBSS) [280] and Hanks' balanced salt solution (HBSS) [281], became known in 1943 and 1949, respectively. In 1950, the history of self-setting calcium orthophosphate formulations was started [282]. 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 1,100 °C, did not set in H_3PO_4, while that in liquid containing 9.6 % CaO was found to set after $\sim$12 h in the presence of H_3PO_4 [282]. The latter mixture might be considered as the first prototype of the self-setting calcium orthophosphate formulations (reviewed in Refs. [283, 284]). The next publications on this topic appeared in 1975 [285] and 1976 [286]. In the latter study, the authors implanted porous cylinders prepared from mixtures of 80 % TTCP + 20 % MCP, 80 % TCP + 20 % MCP, and 80 % DCP + 20 % MCP (it is unclear whether MCP and DCP were hydrated or not and whether α- or β-TCP was used), which could have possessed some self-setting abilities. Therefore, the study by Köster et al. [286] could probably be considered as the first biomedical application of the self-setting calcium orthophosphate formulations. However, the real history of this subject started in 1982 [287, 288].

The modern history of ACP [65] began in 1955 [289], while, in 1960, the first mentioning on CDHA in the publication's title occurred [290]. In 1963, an important study on HA preparation was published [291], while, in 1964, the crystal structure of HA was refined [292]. In 1965, thorough investigations of carbonated apatites were started [293]. In 1969, an important paper on a forming method of HA prostheses was published [294], in which the authors hot-pressed HA power into dense and useful shapes. That study might be considered as the earliest one on the fabrication of calcium orthophosphate implants. In 1971, the first study on preparation of biodegradable porous β-TCP scaffolds was published [295]. Therefore, it is not surprising that the term "bioceramics" has been introduced simultaneously. Namely, according to the available databases, the first paper with the term "bioceramics" in the abstract was published in 1971 [296], while the first papers with that in the title were published in 1972 [297, 298]. However, application of the ceramic materials as prostheses had been known before [299–302]. Also, in 1972 [303] and 1973 [304], the first publications on lunar apatites were published. In 1973, the work of Graham and van der Eb showed the first application of calcium orthophosphates in condensation of genetic materials [305]. The researchers demonstrated that calcium orthophosphates could condense DNA and increase the transfection efficiency with a relatively simple procedure. In addition, in 1973, the first study on preparation and implantation of resorbable and porous calcium orthophosphate (it was β-TCP) bioceramics was published [306]. Besides, in 1973, an important book by McConnell was published [307]. In 1975, the modern dental application of calcium orthophosphates began. Namely, β-TCP was applied both in surgically created periodontal defects [308] and as an adjunct to apical closure in pulpless permanent teeth [309], followed by a study of 1979, in which dense HA cylinders were used for immediate tooth root replacement [310]. On April 26, 1988, the first international symposium on bioceramics was held in Kyoto, Japan.

The history of calcium orthophosphate coatings, films, and layers (reviewed in Refs. [311, 312]) began in 1976 [313], while that of calcium orthophosphate-based biocomposites and hybrid biomaterials (reviewed in Ref. [256]) initiated in 1981 [314, 315]. 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 Jarcho [316–319] in the USA, de Groot [320–322] in Europe, and Aoki [323–326] in Japan. Shortly afterward HA has become a bioceramic of reference in the field of calcium orthophosphates for biomedical applications. The early commercial trademarks, composition, producers, and year comprised Synthograft/Synthos (β-TCP), Miter Inc./J&J (1975); CEROS 80 (HA), Mathys (1980); Durapatite (HA), Cook-Waite (<1981); ProOsteon (coralline HA), Interpore (1981); Alveograf (HA), Cook-Waite (1982); Calcitite (HA), Calcitek (1982); CEROS 82 (β-TCP), Mathys (1982); BioBase (α-TCP), Zimmer (1982); and Periograf (HA), Cook-Waite (<1983) [327]. As seen from this list, preparation and biomedical applications of apatites derived from sea corals [328–330] and bovine bone [331] were already known [332]. In 1985, the first publication on drug-loaded calcium orthophosphate bioceramics [333], as well as those on biphasic, triphasic, and multiphasic calcium orthophosphates (reviewed in Ref. [334]), was published [335, 336]. In 1990, the first version of simulated body fluid (SBF) was introduced [337], while the history of nanodimensional and nanocrystalline calcium orthophosphates (reviewed in Refs. [338, 339]) started in 1994 [340–344]. Finally yet importantly, also in 1994, the first paper on use of calcium orthophosphates as scaffolds was published [345], while applications of calcium orthophosphates in tissue engineering began in 1998 [346–348].

To finalize the twentieth century, it is important to mention the early books on the subject. The earliest collected book of 1983 was edited by de Groot [322], followed by a book of 1984 edited by Misra [349], while three most important monographs on apatites and other calcium orthophosphates were published in 1991 by LeGeros [350] and Aoki [351], as well as in 1994 by Elliott [352]. To get further details on the recent history of calcium orthophosphates, bioceramics, and biomaterials in general, the interested readers are referred to other reviews on the subject [10, 12–15, 250, 262–265].

15.6 Conclusions

To finalize this chapter, let me cite Wikipedia once again: “Historians write in the context of their own time, and with due regard to the current dominant ideas of how to interpret the past, and sometimes write to provide lessons for their own society” [9]. Therefore, all the aforementioned historical facts, discoveries, theories, concepts, misconceptions, and approaches are treated according to the current (AD 2013) level of knowledge on calcium orthophosphates. Thus, it is important to bear in mind that the reported treatment of the historical facts and events might be reconsidered in the future due to both new discoveries and updated points of view. Nevertheless, some solid statements can be made.

The subject of apatites and other calcium orthophosphates has been investigated for almost 250 years. This was a long period of great discoveries and impressive mistakes, original concepts and interesting misconceptions, excellent experiments, and various unfortunates initially of the calcified tissues only and afterward of the chemically pure apatites and other calcium orthophosphates. All these years were spent on gaining the initial knowledge on the subject, followed by its further clarification, extension, and development. These eventful years were full of daily and routine hard work performed by many excellent and of moderate abilities scientists and researchers, students and assistants, technicians, and participants, the vast majority of whom have not even been mentioned in this chapter. Nevertheless, by 1950, the combined long-term efforts of all these often-unknown early investigators created the solid background for a real explosion of science, technology, and biomedical applications of apatites and other calcium orthophosphates that started in the 1960s and continuously prospers up to now, which, finally, resulted in the current state of the art.

As seen from the previously mentioned, the substantial amount of currently available 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 information. Since the first commercially produced artificial bone grafts and other types of calcium orthophosphate-containing biomaterials appeared just a few decades ago [316–327], a reasonable question arises: why did it take so long (almost 200 years) to translate the initial knowledge into practice? Presumably, this is a matter of the technological development because both the biomedical and mechanical properties of even the most advanced formulations are still unsatisfactory and incomparable with those of natural bones and teeth. Hopefully, the reported historical overview provides the necessary background that will keep encouraging natural scientists, engineers, and clinicians to rethink and reinvestigate the already forgotten and poorly known facts and approaches for further development of calcium orthophosphate-based formulations.

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