1
Bioceramics – A Historical Perspective

Synopsis

In this chapter, we will attempt to trace briefly the long and sometimes anfractuous history of important bioceramics including coatings. Emphasis will be put on the bioinert ceramics alumina and zirconia, as well as on bioactive, that is osseoconductive calcium phosphates.

1.1
Alumina

Alum (potassium aluminium sulfate, $KAl(SO_4)_2 \cdot 12H_2O$) was already known in antiquity ('sal sugoterrae' of Pliny), and widely utilised in dying of wool, as a coagulant to reduce turbidity in water, and as a medicine to remedy various ailments based on its astringent, haemostatic and antibiotic nature. In 1754, the German (al)chemist Andreas Sigismund Marggraf (1709–1782) was first to isolate aluminium oxide ('Alaunerde') from alum but was unable to determine its exact composition (Marggraf, 1754, 1761). Between 1808 and 1810, Sir Humphrey Davy tried unsuccessfully to reduce the oxide to metallic aluminium, a feat that was accomplished later by Oerstedt (1825) by heating aluminium chloride with potassium amalgam.

Aluminium oxide (alumina) has also been known since ancient times and several isolated uses have been reported for emery (smirgel), an impure corundum occurring, for example, on the Greek island of Naxos. Gorelick and Gwinnett (1987) have shown that emery was likely employed as an abrasive for drilling of hardstone beads and cylinder seals during ancient Mesopotamian times. In addition, finely ground emery powder was arguably used by the famous Greek sculptor Pheidias as a separation medium to avoid adhesion of heated glass sheets to clay-based moulds. The corrugated glass sheets thus obtained were likely designed to be clothing folds adorning the *himation* (ancient Greek cloak) of the giant statue of Zeus in his Olympia temple (Heilmeyer, 1981).

The unique mechanical and thermal properties of alumina have spurred its utilisation as high temperature-, wear- and corrosion-resistant ceramics. Besides this,

Bioceramic Coatings for Medical Implants: Trends and Techniques, First Edition.
Robert B. Heimann and Hans D. Lehmann.

its first application as biomaterial was suggested by Rock (1933) in a Deutsches Reichspatent, followed by a patent issued to Sandhaus (1966) for the use of alumina for dental and jaw implants. However, it was only after the groundbreaking paper by Boutin (1972) that alumina took off on its worldwide triumphal course as a suitable ceramic material for femoral balls of hip endoprostheses.

Figure 1.1 shows the development of bioinert and bioactive ceramics (Rieger, 2001). In 1920, tricalcium phosphate (TCP) was suggested as a bioresorbable ceramic material for filling of bone gaps that, however, was unable to bear extended loads (Heughebaert and Bonel, 1986). Alumina entered the scene around 1930 (Rock, 1933) and was subsequently much improved in terms of its compressive strength and fracture toughness by painstaking engineering of its purity and ever decreasing grain size down to the nano-scale level. This development led to orthopaedic structural ceramic products such as Ceraver-Osteal® (Boutin, 1972), Keramed® (Glien, Kerbe and Langer, 1976), Frialit® (Griss and Heimke, 1981), and finally the family of Biolox® ceramics by Feldmühle, later CeramTec companies (Dörre and Dawihl, 1980, see also Clarke and Willmann, 1994) as well as BIONIT® manufactured by Mathys Orthopädie GmbH (Bettlach, Switzerland). The current high-end product of CeramTec is Biolox® delta, a zirconia-toughened alumina (ZTA) alloy reinforced with chromia as a crack arrester (see Chapter 4.1.1).

Evaluation of biocompatibility resulted chiefly from clinical experience (Boutin, 1972; Hulbert, Morrison and Klawitter, 1972; Griss *et al.*, 1973; Griss, 1984; Mittelmeier, Heisel and Schmitt, 1987) supported by *in vitro* cytotoxicity testing (for example Catelas *et al.*, 1998; Nkamgueu *et al.*, 2000, and many other contributors).

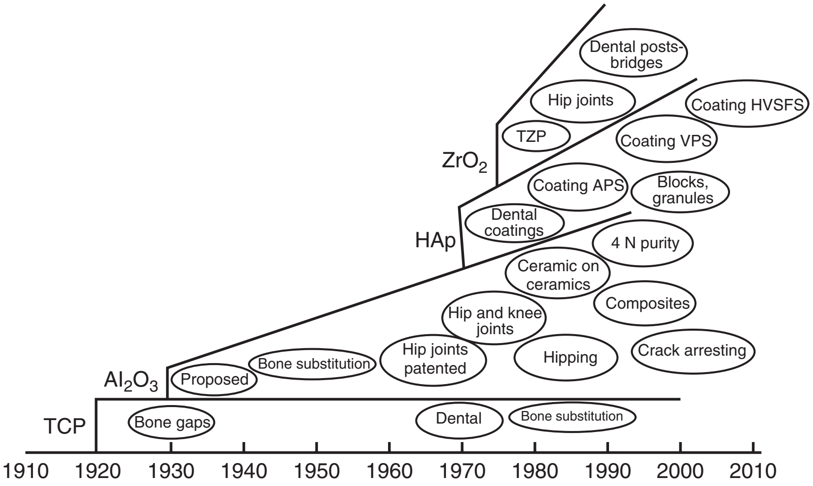

Figure 1.1 Application of bioceramics in medical devices: 100 years of history. (Adapted from Rieger (2001), and adjusted to current developments.)

1.2
Zirconia

Zirconium dioxide was first extracted from the mineral zircon (zirconium silicate, $ZrSiO_4$) by the German chemist Martin Heinrich Klaproth (1743–1817) in 1787, using the yellowish orange-coloured, transparent gemstone jacinth (hyacinth) from Ceylon as starting material. Zircon has been known to man for a very long time; its name presumably originated from the Arabian word 'zargun', meaning 'gold-coloured' that etymologically is related to the ancient Persian words 'zarenu' (gold) and 'gauna' (colour) (Vagkopoulou *et al.*, 2009). In 1824, the Swedish chemist Jöns Jakob Berzelius (1779–1848) was first to isolate metallic zirconium by reduction of K_2ZrF_6 with potassium.

For the following 150 years, zirconium as well as zirconia were considered mere scientific curiosities without any substantial technological merits apart from limited utilisation of zirconia in heavy-duty bricks for high temperature applications and for special glasses (Morey, 1938) with a high index of refraction. It was only in 1969 that the first scientific study of the outstanding biomedical properties of zirconia emerged (Helmer and Driskell, 1969). Subsequently, it was discovered that alloying zirconia with oxides such as yttria, calcia, magnesia and others was able to stabilise its tetragonal modification thus halting the structurally and mechanically deleterious phase transition from the tetragonal to the monoclinic phase (Garvie and Nicholson, 1972). This discovery allowed using the so-called transformation toughening of zirconia to produce ceramics with unsurpassed crack resistance ('ceramic steel') (Garvie, Hannink and Pascoe, 1975). Still later, it was found that even unalloyed microcrystals of zirconia could be stabilised against transformation if the tetragonal high temperature phase has a reduced surface free energy with respect to the monoclinic low temperature structure (Garvie, 1978). These partially stabilised tetragonal zirconia polycrystalline ceramics (TZP) are characterised by a structure of high density, small grain size and high purity that jointly elicit strength and fracture toughness unusually high for a ceramic material. Consequently, such ceramics were employed to fashion femoral ball heads starting by the mid-eighties of the past century (Cales and Stefani, 1995, Figure 1.1) and, later, to make dental parts of all kinds including dental roots, inlays and veneers.

Starting in the 1980s, besides structural and mechanical investigations of zirconia (see, for example Rühle, Claussen and Heuer, 1983), studies on its biocompatibility moved into the limelight as evidenced, for example, by the pioneering work of Garvie *et al.* (1984), Christel *et al.* (1989) and Hayashi *et al.* (1992). Their work triggered a virtual avalanche of research that used increasingly sophisticated evaluation techniques of material properties. In addition, studying the *in vitro* and *in vivo* biomedical performance of zirconia in contact with biofluid and tissues established zirconia as a viable bioceramics (for example Piconi and Maccauro, 1999; Piconi *et al.*, 2003; Fini *et al.*, 2000; Clarke *et al.*, 2003; Thamaraiselvi and Rajeswari, 2004; Manicone, Rossi Iommetti and Raffaeli, 2007; Afzal, 2014). Later, several applications emerged as bond coats as well as reinforcing particles for hydroxyapatite coatings for implants.

Today, a large segment of utilisation of zirconia as colour-adapted tooth veneers in dental restoration exists (Cales, 1998). At this point, it is appropriate to mention the ancient French dental doctor Pierre Fauchard (1678–1761) who may be considered the vanguard of modern tooth restoration. He has been credited with recognising the potential of porcelain enamels and initiating research with porcelain to imitate the natural colour of teeth and gingival tissue (Fauchard, 1728).

1.3
Calcium Phosphates

Calcium orthophosphates have been known to be associated with organic tissue, diligently researched and eventually applied for at least 250 years. As early as 1769, the Swedish chemists Johan Gottlieb Gahn and Carl Wilhelm Scheele discovered that TCP, $Ca_3(PO_4)_2$ could be obtained by burning bone, and they continued to isolate elemental phosphorus by reducing acid-treated bone ash with charcoal, and distilling off the escaping phosphorus vapour in a retort (Threlfall, 1951). In fact, bone ash was the predominant source of phosphorus until the 1840s when mining, first of tropical island deposits formed from bird and bat guano and, later phosphate rock, took over.

The preparation of pure tricalcium orthophosphate by an alternate route was already described 200 years ago in an encyclopaedia as follows:

> *Phosphate of lime, proper. As this salt constitutes the basis of bones, it is not necessary to prepare it artificially. It may be obtained in a state of purity by the following process: Calcine the bones to whiteness, reduce them to powder, and wash them repeatedly with water, to separate several soluble salts, which are present. Dissolve the whole in muriatic acid, and precipitate by means of ammonia. The precipitate, when well washed and dried, is pure phosphate of lime* (Good, Olinthus and Newton, 1813).

A chemistry textbook for students of medicine written in 1819 (Bache, 1819) states:

> *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 white semi-transparent porcelain.*

Heated and crushed animal bones were used copiously in making bone China, predominately in Britain, commencing around the mid-eighteenth century (Heimann, 2012; Heimann and Maggetti, 2014). As it turned out, by the end of the eighteenth century much research had been performed on calcium phosphates, which involved the names of many renowned scientists of the time including Klaproth, Proust, Lavoisier, Vauquelin and de Fourcroy. Recently, these research activities were exhaustively summarised by Dorozhkin (2013).

The nineteenth century saw increasingly important research on calcium phosphates, culminating in a series of contributions by Mitscherlich (1844), Berzelius (1845), Fresenius (1867), Warington (1871) and Church (1873). In our context, particular attention has to be paid to Warington's paper that describes the dissolution of bone ash in the presence of carbonated water, an important precondition for the agricultural use of calcium phosphates, and to the contribution by Church who was presumably the first to determine and publish the exact formula of fluorapatite.

The knowledge of the presence of calcium phosphates in bone (De Fourcroy *et al.*, 1788; Parr, 1809; von Bibra, 1844), teeth (Davy, 1814), blood and milk (De Fourcroy, 1804), urine (De Fourcroy *et al.*, 1788) as well as urinary and renal calculi (Colon, 1770; Pemberton, 1814) was solidly established by the early nineteenth century. Additional historic evidence for this has been painstakingly recorded by the prolific chronicler of calcium phosphates, Dorozhkin (2012), quoting no less than 279 references on the history of calcium phosphate research. Among these treasures there appears faint indication that several calcium phosphate phases, important for biomineralisation, were already known, suspected or suggested early on such as amorphous calcium phosphate, ACP (Brande and Taylor, 1863) and octacalcium phosphate, OCP as well as dicalcium phosphate dihydrate, DCPD (brushite) (Warington, 1866).

The discoveries of X-ray radiation by Röntgen (1895) and its application to crystal structure analysis by Bragg father and son (Bragg, 1921) moved research on calcium phosphates from a descriptive to a predictive acquisition of knowledge, and allowed investigating phase transitions in unprecedented detail. Consequently, a series of studies emerged in early 1930 using X-ray diffraction (XRD) as an important and versatile tool to assess the structural chemistry of calcium phosphates in general and hydroxyapatite in particular (Hendricks *et al.*, 1931; Roseberry, Hastings and Morse, 1931; Trömel, 1932; Bredig, 1933; Bredig, Franck and Füldner, 1933). De Jong (1926) was first to identify the structure of the calcium phosphate phase in bone as being akin to geological apatite that has long been known as an important phosphate mineral (Werner, 1788). From their XRD studies Hendricks *et al.* (1931) concluded that animal bone consisted of carbonate apatite, $Ca_{10}[CO_3(PO_4)_6]\cdot H_2O$, a compound isomorphous with fluorapatite. They also reported the existence of oxyapatite, $Ca_{10}O(PO_4)_6$ that could be prepared by heating hydroxyapatite or bone at 900 °C until constant weight had been attained. The latter finding met with disagreement by Bredig *et al.* (1933) who drafted one of the earliest $CaO-P_2O_5$ phase diagrams in the absence of water, and first proposed the existence of 'mixed' apatites, that is oxyhydroxyapatites $Ca_{10}(PO_4)_6X_{2m}O_n$ ($X = OH, F$; $m + n = 1$). However, they denied the existence of a pure stable oxyapatite structure, because in their opinion the X position could not be left empty. Much later, research refuted this contention (see Chapter 6.2.1.4). Bredig *et al.* (1933) based their conclusion about the non-existence of pure oxyapatite on experimental evidence and went on to postulate the likewise non-existence of TCP with apatite structure, unlike the existence of an isomorphous relationship between pyromorphite, $Pb_{10}(PO_4)_6Cl_2$ and $Pb_3(PO_4)_2$ established by Zambonini and Ferrari (1928). The systematic progress of the knowledge gained on the chemical composition and structure of bone mineral, that is Ca-deficient hydroxyapatite was recently reviewed by Rey *et al.* (2010). The important, but still not quite resolved, role water assumes in the structure of bone was beautifully highlighted by Pasteris (2012).

Considering the importance of the structure of bone as a biocomposite of Ca-deficient defect hydroxyapatite and triple helical strands of collagen I, it is not surprising that as early as about 40 years ago synthetic hydroxyapatite was suggested as a biocompatible artificial material for incorporation in the human body (Jarcho *et al.*, 1976; Jarcho, 1981). In a next step, hydroxyapatite was introduced as a bioactive, that is osseoconductive coating. Its first application was in plasma-sprayed coatings for dental implants, followed by coatings for the stem of hip endoprostheses to improve implant integration with the surrounding bone (Ducheyne *et al.*, 1980; Figure 1.1). Although the preferred deposition technology was and still is atmospheric plasma spraying (APS, León and Jansen, 2009; Heimann, 2010), other techniques abound including low-pressure (vacuum) plasma spraying (VPS, Gruner, 1986) and most recently high-velocity suspension flame spraying (HVSFS, Bolelli *et al.*, 2010). Chapter 5 of this treatise will exhaustively review many deposition techniques. Hydroxyapatite was also utilised in the form of densified implants for dental root replacement (Denissen and de Groot, 1979), as a suitable material for filling bone cavities, and for fashioning skeletal prostheses (Hulbert *et al.*, 1970; Capello and Bauer, 1994).

In 2003, an up-to-date summary of studies was edited by Epinette and Manley (2003), describing the state-of-the-art of hydroxyapatite coatings in orthopaedics as this stood at the close of 2002. This compilation of results was designed to help to answer the still somewhat hotly debated question of whether the favourable results achieved in the short term with this method of biologic fixation of total joint implants has withstood the test of time. The goal of Epinette and Manley's book was mainly to determine if the use of hydroxyapatite coatings for the fixation of orthopaedic implants to bone has been proven by the survivorship and satisfaction of those patients who had received hip and knee implants.

References

Afzal, A. (2014) Implantable zirconia bioceramics for bone repair and replacement: a chronological review. *Mater Express*, **4** (1), 1–12.

Bache, F. (1819) *A System of Chemistry for the Use of Students of Medicine*, Printed and published for the author William Fry, Philadelphia, PA, 624 pp.

Berzelius, J. (1845) Über basische phosphorsaure Kalkerde. *Justus Liebigs Ann. Chem.*, **53** (2), 286–288.

Bolelli, G., Cannillo, V., Gadow, R., Killinger, A., Lusvarghi, L., Sola, A., and Stiegler, N. (2010) Microstructure and in-vitro behaviour of a novel high-velocity suspension flame sprayed (HVSFS) bioactive glass coating. *Surf. Coat. Technol.*, **205** (4), 1145–1149.

Boutin, P. (1972) L'arthroplastie total de la hanche par prothèse en alumine frittée. *Rev. Chir. Orthop.*, **58**, 229–246.

Bragg, W.H. (1921) Application of the ionisation spectrometer to the determination of the structure of minute crystals. *Proc. Phys. Soc. London*, **33**, 222–224.

Brande, W.T. and Taylor, A.S. (1863) *Chemistry*, Blanchard and Lea, Philadelphia, PA.

Bredig, M.A. (1933) Zur Apatitstruktur der anorganischen Knochen- und Zahnsubstanz. Hoppe-Seyler's. *Z. Physiol. Chem.*, **216** (5-6), 239–243.

Bredig, M.A., Franck, H.H., and Füldner, H. (1933) Beiträge zur Kenntnis der Kalk-Phosphorsäure-Verbindungen II. *Z. Elektrochem.*, **39** (12), 959–969.

Cales, B. (1998) in *Bioceramics 11* (eds T.Z. LeGeros and J.P. LeGeros), World Scientific Publishing, New York, pp. 591–594.

Cales, B. and Stefani, Y. (1995) *Encyclopedic Handbook of Biomaterials and Bioengineering, Part B: Applications*, vol. 1, Marcel Dekker, Inc., New York, Basel, Hong Kong, pp. 415–452.

Capello, W.N. and Bauer, T.W. (1994) in *Bone Implant Interfaces* (ed. H.U. Cameron), Mosby, St. Louis, MO, Baltimore, MD, Boston, MA, pp. 191–202. ISBN: 0-8016-6483-7.

Catelas, I., Huk, O.L., Petit, A., Zukor, D.J., Marchand, R., and Yahia, L. (1998) Flow cytometric analysis of macrophage response to ceramic and polyethylene particles: effects of size, concentration, and composition. *J. Biomed. Mater. Res.*, **41** (4), 600–607.

Christel, P., Meunier, A., Heller, M., Torre, J.P., and Peille, C.N. (1989) Mechanical properties and short-term in-vivo evaluation of yttrium oxide-partially-stabilized zirconia. *J. Biomed. Mater. Res.*, **23** (1), 45–61.

Church, A.H. (1873) New analyses of certain mineral arseniates and phosphates. 1. Apatite; 2. Arseniosiderite; 3. Childrenite; 4. Ehlite; 5. Tyrolite; 6. Wavellite. *J. Chem. Soc.*, **26**, 101–111.

Clarke, I.C., Manaka, M., Green, M.S., Williams, P., Pezotti, G., Kim, Y.-H., Ries, M., Sugano, N., Seidel, L., Delauney, C., Ben Nissan, B., Donaldson, T., and Gustavson, G.A. (2003) Current status of zirconia used in total hip implants. *J. Bone Joint Surg.*, **85A** (Suppl. 4), 73–84.

Clarke, I.C. and Willmann, G. (1994) in *Bone Implant Interfaces* (ed. H.U. Cameron), Mosby, St. Louis, MO, Baltimore, MD, Boston, MA, pp. 203–252. ISBN 0-8016-6483-7.

Colon, P. (1770) *De calculo Renali, theses Anatomicae et Chirurgicae*, Le Prieur [etc.], Paris.

Davy, H. (1814) *Conversations on Chemistry, in which the Elements of that Science are Familiarly Explained and Illustrated by Experiments and Plates*, Didnep's Press [etc.] (quoted after Dorozhkin, 2012).

De Fourcroy, A.F. (1804) *A General System of Chemical Knowledge and its Application to the Phenomena of Nature and Art*, 11 vols, vol. 3, (Translated by W. Nicholson), London, Cadell & Davies.

De Fourcroy, A.T. *et al.* (1788) *Elements of Natural History, and of Chemistry*, being the second edition of the elementary lectures on those sciences, first published in 1782, and now greatly enlarged and improved, by the Author, M. de Fourcroy, doctor of the faculty of medicine at Paris, of the Royal Academy of Sciences, andc, andc, andc, Translated into English. With occasional notes, and an historical preface, by the translator, vol. IV, G.G.J. and J. Robinson, Pater-Noster-Row, London, 465 pp. (quoted after Dorozhkin, 2012).

De Jong, W.F. (1926) La substance minerale dans les os. *Recl. Trav. Chim. Pays-Bas Belg.*, **45**, 445–448.

Denissen, H.W. and de Groot, K. (1979) Immediate dental root implants from synthetic dense calcium hydroxylapatite. *J. Prosth. Dent.*, **42** (5), 551–556.

Dorozhkin, S.V. (2012) in *Calcium Phosphate. Structure, Synthesis, Properties, and Applications*, Biochemistry Research Trends (ed. R.B. Heimann), Nova Science Publishers, New York, pp. 1–40. ISBN: 978-1-62257-299-1

Dorozhkin, S.V. (2013) A detailed history of calcium orthophosphates from 1770s till 1950. *Mater. Sci. Eng. C*, **33** (6), 3085–3110.

Dörre, E. and Dawihl, W. (1980) in *Mechanical Properties of Biomaterials* (eds P. Ducheyne and G.W. Hastings), John Wiley & Sons, Ltd, Chichester, pp. 113–127.

Ducheyne, P., Hench, L.L., Kagan, A., Martens, M., Mulier, J.C., and Burssens,

A. (1980) The effect of hydroxyapatite impregnation on bonding of porous coated implants. *J. Biomed. Mater. Res.*, **14**, 225–237.

Epinette, J.A. and Manley, M.T. (2003) *Fifteen Years of Clinical Experience with Hydroxyapatite Coatings in Joint Arthroplasty*, Springer. ISBN: 978-2-2070-0508-4.

Fauchard, P. (1728) *Le chirurgien dentiste ou Traite des dents* (engl. transl. by Lindsay, L. (1946) *The Surgeon Dentist*, Butterworth & Co, London.

Fini, M., Giavaresi, G., Aldini, N.N., Torricelli, P., Morrone, G., Guzzardella, G.A., Giardino, R., Krajewski, A., Ravaglioli, A., Belmonte, M.M., Benedittis, A.D., and Biagini, G. (2000) The effect of osteopenia on the osteointegration of different biomaterials: histomorphometric study in rats. *J. Mater. Sci.: Mater. Med.*, **11** (9), 579–585.

Fresenius, R. (1867) Über die Bestimmung der Phosphorsäure im Phosphorit nebst Mittheilung der Analysen des Phosphorits und Staffelits aus dem Lahnthal. *Z. Analyt. Chem.*, **6**, 403–409.

Garvie, R.C. (1978) Stabilization of the tetragonal structure in zirconia microcrystals. *J. Phys. Chem.*, **82** (2), 218–224.

Garvie, R.C., Hannink, R.H.J., and Pascoe, R.T. (1975) Ceramic steel? *Nature*, **258**, 703–704.

Garvie, R.C. and Nicholson, P.S. (1972) Structure and thermodynamical properties of partially stabilized zirconia in the CaO-ZrO_2 system. *J. Am. Ceram. Soc.*, **55**, 152–157.

Garvie, R.C., Urbani, C., Kennedy, D.R., and McNeuer, J.C. (1984) Biocompatibility of Mg-PSZ ceramics. *J. Mater. Sci.*, **19** (10), 3224–3228.

Glien, W., Kerbe, F., and Langer, G. (1976) Keramik in der Chirurgie. *Hermsdorfer Techn. Mitt.*, **16**, 445.

Good, J.M., Olinthus, G., and Newton, B. (1813) *Pantologia: A New Cyclopædia, Comprehending a Complete Series of Essays, Treatises, and Systems, Alphabetically Arranged; with a General Dictionary of Arts, Sciences, and Words: the Whole Presenting a Distinct Survey of Human Genius, Learning, and Industry*, vol. IX. P – PYX, G. Kearsley, London.

Gorelick, L. and Gwinnett, A.J. (1987) A history of drills and drilling. *NY State Dent. J.*, **53** (1), 35–39.

Griss, P. (1984) in *Fundamental Behaviour of Orthopedic Biomaterials*, Vol. II: Applications, CRC Series in Structure-Property Relationships of Biomaterials (eds P. Ducheyne and G.W. Hastings), CRC Press, Boca Raton, FL, pp. 22–43.

Griss, P., von Adrian-Werburg, H., Krempien, B., and Heimke, G. (1973) Biological activity and histocompatibility of dense Al_2O_3/MgO ceramic implants in rats. *J. Biomed. Mater. Res.*, **7** (3), 453–462.

Griss, P. and Heimke, G. (1981) in *Biocompatibility of Clinical Implant Materials*, CRC Series in Biocompatibility, vol. 1 (eds D.F. Williams *et al.*), CRC Press, Boca Raton, FL, pp. 156–198.

Gruner, H. (1986) Coating of an implant body. Intern. Patent Appl. WO 1986/006617 A1.

Hayashi, K., Matsuguchi, N., Uenoyama, K., and Sugioka, Y. (1992) Re-evaluation of the biocompatibility of bioinert ceramics in vivo. *Biomaterialia*, **13** (4), 195–200.

Heilmeyer, W.-D. (1981) Antike Werkstattfunde in Griechenland. *Archäolog. Anzeiger*, 440–453.

Heimann, R.B. (2010) *Classic and Advanced Ceramics. From Fundamentals to Applications*, Wiley-VCH Verlag GmbH, Weinheim. ISBN: 978-3-527-32517-7.

Heimann, R.B. (2012) in *Calcium Phosphate. Structure, Synthesis, Properties, and Applications*, Biochemistry Research Trends Series (ed. R.B. Heimann), Nova Science Publishers, New York, pp. 467–473.

Heimann, R.B. and Maggetti, M. (2014) *Ancient Ceramics. Materials, Technology, Art, and Culinary Traditions*, Chapter 16, Schweizerbart Science Publishers, Stuttgart.

Helmer, J.D. and Driskell, T.D. (1969) Research on bioceramics. Symposium on Use of Ceramics as Surgical Implants, Clemson University, Clemson, SC.

Hendricks, S.B., Hill, W.A., Jakobs, K.D., and Jefferson, M.E. (1931) Structural characteristics of apatite-like substances and composition of phosphate rock and bone as determined from microscopical and X-ray examinations. *Ind. Eng. Chem.*, **23** (12), 1413–1418.

Heughebaert, J.C. and Bonel, G. (1986) in *Biological and Biomechanical Performance of Biomaterials* (eds P. Christel, A. Meunier, and A.J.C. Lee), Elsevier, Amsterdam, pp. 9–14.

Hulbert, S.F., Morrison, S.J., and Klawitter, J.J. (1972) Tissue reaction to three ceramics of porous and non-porous structures. *J. Biomed. Mater. Res.*, **6** (5), 347–374.

Hulbert, S.F., Young, F.A., Matthews, R.S., Klawitter, J.J., Talbert, C.D., and Stelling, F.H. (1970) Potential of ceramic materials as permanently implantable skeletal prostheses. *J. Biomed. Mater. Res.*, **4** (3), 433–456.

Jarcho, M. (1981) Calcium phosphate ceramics as hard tissue prosthetics. *Clin. Orthop. Relat. Res.*, **157**, 259–278.

Jarcho, M., Bolen, C.H., Thomas, M.B., Bobick, J., Kay, J.F., and Doremus, R.H. (1976) Hydroxylapatite synthesis and characterization in dense polycrystalline form. *J. Mater. Sci.*, **11**, 2027–2035.

Klement, R. and Trömel, G. (1932) Hydroxylapatit, der Hauptbestandteil der anorganischen Knochen- und Zahnsubstanz Hoppe-Seyler's. *Z. Physiol. Chem.*, **213**, 263–269.

León, B. and Jansen, J.A. (2009) *Thin Calcium Phosphate Coatings for Medical Implants*, Springer, New York. ISBN: 978-0-387-77718-4.

Manicone, P.F., Rossi Iommetti, P., and Raffaeli, L. (2007) An overview of zirconia ceramics: properties and clinical applications. *J. Dent.*, **35** (11), 819–826.

Marggraf, A.S. (1754) De l'alun. Memor. Acad. Sci. Berlin, **X**, 31-51.

Marggraf, A.S. (1761) Versuche mit der Alaun-Erde. *Chym. Schriften, 1. Theil, Kap.*, **12**, 212 ff.

Mitscherlich, E. (1844) *Lehrbuch der Chemie*, Band 1: Die Metalloide, 4th edn, Berlin E.S.Mittler.

Mittelmeier, H., Heisel, J., and Schmitt, E. (1987) *Primär- und Revisions-Alloarthroplastik Hüft- und Kniegelenke*, Springer, Berlin, Heidelberg, pp. 103–116.

Morey, G.W. (1938) *Properties of Glass*, ACS Monograph Series, vol. 77, Reinhold Publishing Corporation, New York.

Nkamgueu, E.M., Adnet, J.J., Bernard, J., Zierold, K., Kilian, L., Jallot, E., Benhayoune, H., and Bonhomme, P. (2000) *In vitro* effects of zirconia and alumina particles on human blood monocyte–derived macrophages: X-ray microanalysis and flow cytometric studies. *J. Biomed. Mater. Res.*, **52** (4), 587–594.

Parr, B. (1809) *The London Medical Dictionary*, vol. 1, J. Johnson, London.

Pasteris, J.D. (2012) in *Calcium Phosphate. Structure, Synthesis, Properties, and Applications*, Biochemistry Research Trends Series (ed. R.B. Heimann), Nova Science Publishers, New York, pp. 63–94.

Pemberton, C.R. (1814) *A Practical Treatise on Various Diseases of the Abdominal Viscera*, 3rd edn, revised and corrected, Bulmer and Company, London.

Piconi, C. and Maccauro, G. (1999) Zirconia as biomaterial. *Biomaterialia*, **20** (1), 1–25.

Piconi, C., Maccauro, G., Muratori, F., and Brach del Prever, E. (2003) Alumina and zirconia ceramics in joint replacement. *J. Appl. Biomater. Biomech.*, **1** (1), 19–32.

Rey, C., Combes, C., Drouet, C., and Glimcher, M.J. (2010) Bone mineral: update on chemical composition and structure. *Osteoporosis Int.*, **20** (6), 1013–1021.

Rieger, W. (2001) in *World Tribology Forum in Arthroplasty* (eds C. Rieker, S. Oberholzer, and U. Wyss), Hans Huber, Bern, pp. 309–318.

Rock, M. (1933) Künstliche Ersatzteile für das Innere und Äussere des menschlichen und tierischen Körpers. Deutsches Reichspatent DRP 583 589, 24 August 1933.

Röntgen, W.C. (1895) Über eine neue Art von Strahlen (Vorläufige Mittheilung). *Sitzungsber. Würzb. Phys. Med. Ges.*, **137**, 132–141.

Roseberry, H.H., Hastings, A.B., and Morse, J.K. (1931) X-ray analysis of bone and teeth. *J. Biol. Chem.*, **90**, 395–407.

Rühle, M., Claussen, N., and Heuer, A.H. (1983) *Science and Technology of Zirconia II*, Advances in Ceramics, vol. 12, American Ceramic Society, 842 pp. ISBN: 978-0-9160-9464-5.

Sandhaus, S. (1966) Bone implants, and drills and tapes for bone surgery. EP 1083769 (A), application date Mar. 11, 1966, UK.

Thamaraiselvi, T.V. and Rajeswari, S. (2004) Biological evaluation of bioceramic materials – A review. *Trends Biomater. Artif. Organs*, **18** (1), 9–17.

Threlfall, R.E. (1951) *The Story of 100 Years of Phosphorus Making: 1851–1951*, Albright & Wilson Ltd, Oldbury.

Trömel, G. (1932) Untersuchungen über die Bildung eines halogenfreien Apatits aus basischen Calciumphosphaten. *Z. Physiol. A*, **158**, 422–432.

Vagkopoulou, T., Koutayas, S.O., Koidis, P., and Strub, J.R. (2009) Zirconia in dentistry: Part 1. Discovering the nature of an upcoming bioceramic. *Eur. J Esthetic Dentistry*, **4** (2), 130–151.

Von Bibra, E. (1844) *Chemische Untersuchungen über die Knochen und Zähne des Menschen und der Wirbelthiere*, Kunstverlag, Schweinfurt.

Warington, R. Jr., (1866) Researches on the phosphates of calcium, and upon the solubility of tricalcic phosphate. *J. Chem. Soc.*, **19**, 296–318.

Warington, R. Jr., (1871) On the solubility of the phosphates of bone-ash in carbonic water. *J. Chem. Soc.*, **24**, 80–83.

Werner, A.G. (1788) Geschichte, Karakteristik, und kurze chemische Untersuchung des Apatits. *Bergmännisches J.*, **1**, 76–96.

Zambonini, F. and Ferrari, A. (1928) Ricerche sul fosfato e sul clorofosfato de piombo (piromorfite). *Atti R. Accad. Lincei Rend. (Roma), Ser. 6*, **7**, 283–291.