

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 osseo-conductive calcium phosphates.

1.1

Alumina

Alum (potassium aluminium sulfate, $\text{KAl}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$) 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,

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).

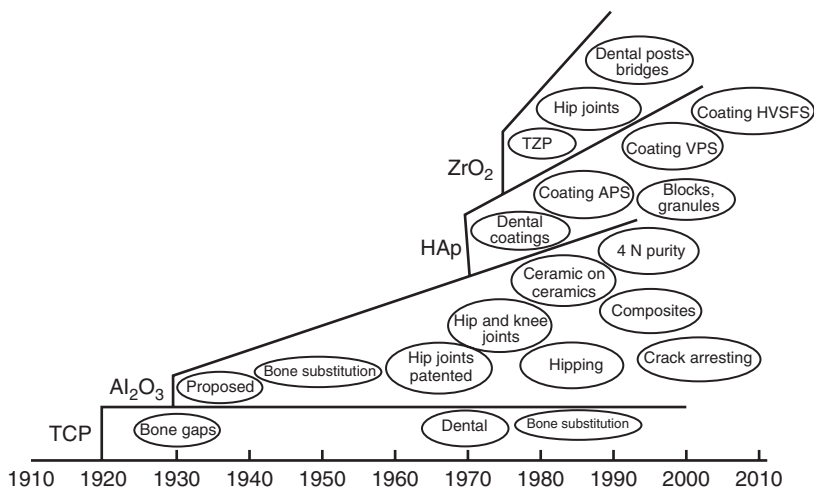


Figure 1.1 Application of bioceramics in medical devices: 100 years of history. (Adapted from Rieger (2001), and adjusted to current developments.)

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 Raffaelli, 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, $\text{Ca}_3(\text{PO}_4)_2$ 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 Földner, 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, $\text{Ca}_{10}[\text{CO}_3(\text{PO}_4)_6] \cdot \text{H}_2\text{O}$, a compound isomorphous with fluorapatite. They also reported the existence of oxyapatite, $\text{Ca}_{10}\text{O}(\text{PO}_4)_6$ 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 $\text{CaO}-\text{P}_2\text{O}_5$ phase diagrams in the absence of water, and first proposed the existence of 'mixed' apatites, that is oxyhydroxyapatites $\text{Ca}_{10}(\text{PO}_4)_6\text{X}_{2m}\text{O}_n$ ($\text{X} = \text{OH}, \text{F}; m + n = 1$). 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, $\text{Pb}_{10}(\text{PO}_4)_6\text{Cl}_2$ and $\text{Pb}_3(\text{PO}_4)_2$ 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 osseointegrative 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.

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