Heritage Science

REVIEW

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History of dental biomaterials: biocompatibility, durability and still open challenges

Elia Marin[1,2,3,4*]

Abstract

Objective This review paper aims to provide a comprehensive understanding of the historical evolution of dental biomaterials, as well as to understand the reasons behind their biocompatibility and to identify the key factors that have influenced their development and use over the past 5000 years.

Data sources The sources for this review were primarily obtained through Scopus and other online databases, such as Google Scholar, which were searched for relevant publications spanning clinical, archeological, and materials science literature. In cases where no other sources were available, information was gathered through consultation with museums and owners of private collections.

Study selection Our search was conducted using specific materials and ages as keywords and, for the last two centuries, retrieving scientific articles written at that time of the first development and commercialization. When possible, secondary sources such as literature reviews were prioritized, while not peer-reviewed documents were utilized only when no other sources were available. References with varying perspective and findings were included, also when presented contradictory or controversial information.

Conclusions In this review, clinical, archeological and chemical data could be merged into a comprehensive analysis of the historical evolution of the concept of biocompatibility in dental materials. The results of this review emphasize the significant advances that have been made in the field of dental biomaterials in terms of biocompatibility, from the use of gold and other metals in ancient civilizations to the development of modern materials such as resin composites and ceramics.

Clinical significance By analyzing the development and use of dental biomaterials over the centuries from clinical, archeological and chemical perspectives, the review sheds light on the key factors that have shaped our understanding of biocompatibility in dental materials and the importance of this concept in the success of dental restorations.

Keywords Dental materials, Biomaterials, History, Challenges, Definitions

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Background

Despite the lack of understanding about the mechanisms of interaction between materials and biological environments, humans have been making and using dental appliances and dental implants for thousands of years [1].

Depending on the geographical location, the level of technological advancement and the customs of the population, these devices could have a purely aesthetic [2] or a more practical [3] function.

In recent years, historical reviews on dental materials have been focused mainly on two complementary aspects: on one side, many authors (mainly anthropologists and archeologists) were interested in the historical and anthropological meanings behind archeological findings [4] dating back hundreds if not thousands of years [5, 6], while on the other side scholars (mainly medical practitioners) preferred to focus on recent history [7], mainly covering medical practices [8–10] and focusing on surgical and post-operative aspects.

This review, covering over 40 materials in a span of more than 4 millennia, takes a different direction: looking more in detail into the materials that were applied and the reasons behind their successes and failures, it aims at showing how the concept of biocompatibility developed and what were the challenges that the practitioners faced as society evolved, up to the middle of the twentieth century.

Thanks to the constant improvements in the fields material science, dentistry, physiology and microbiology, the second half of the twentieth century, as well as the twenty-first century, saw a rapid evolution and expansion of biomaterials, leading to a remarkable array of innovations. These biomaterials, ranging from polymers and ceramics to metals and composites, have found applications across diverse medical disciplines, revolutionizing treatments and enhancing patient outcomes.

Biomaterial science, particularly in relation to the oral cavity, underwent significant advancements during this period, marking a transition to maturity. This review encapsulates the pivotal milestones that lead to this transition into what can be called "the modern era of biomaterial science."

The contents of this review are aimed at a multidisciplinary audience, spanning from material science to dentistry, anthropology and heritage science. By understanding the nature and scope of the materials and devices explored in this review, readers can gain a better comprehension of the evolution of dental sciences and its implications for human society. Furthermore, the contents of this review serve as a resource for precisely categorizing, understanding, and conserving artifacts currently housed in museums and private collections. This is particularly significant due to the relatively frequent presence of spurious specimens within this field, which can lead to misconceptions regarding their true nature and historical significance.

Applications of oral healthcare materials

For the sake of this review, the following definitions will be used when speaking about the applications of the various biomaterials:

Aesthetic modifications: "aesthetic modifications" specifically pertain to interventions that are carried out solely to improve the visual aesthetics of a person's teeth, such as stone inlays or tooth filing;

Amalgams: "amalgams" in dentistry are durable dental restorative materials composed of a mixture of metals, typically including silver, tin, copper, and mercury. These amalgam alloys are used to fill cavities caused by tooth decay. When the amalgam mixture is placed into the prepared cavity, it hardens and forms a strong, long-lasting restoration that effectively restores tooth function and resists wear over time;

Braces: "braces" in dentistry are orthodontic devices used to correct misaligned teeth and jaw structures. They consist of brackets, wires, and often other components that work together to apply controlled forces to gradually move teeth into more optimal positions;

Bridges: "dental bridges" are fixed prosthetic devices used in dentistry to replace missing teeth. They consist of artificial teeth anchored between adjacent natural teeth or dental implants, restoring both function and aesthetics;

Dentures: "dentures" are removable dental prostheses used to replace multiple missing teeth or a complete dental arch. They consist of artificial teeth, usually offering both functional and aesthetic restoration;

False tooth: the term "false tooth" refers to any artificial device that is used in substitution of natural tooth;

Fillings: "fillings" are dental treatments that involve the use of biocompatible materials to repair cavities and damaged tooth structures;

Implants: "dental implants" are used to replace missing teeth by surgically placing artificial "tooth roots" into the jawbone. Modern implants are composed of three parts: a post that is inserted into the jawbone, a crown and an abutment to connect the two;

Obturators: "obturators" are prosthetic devices used in dentistry to close or block defects in the roof of the oral cavity, such as gaps resulting from surgical procedures, congenital anomalies, or trauma;

Prosthetic restorations: "prosthetic restoration" refers to the process of replacing missing or damaged teeth with artificial substitutes that are designed to mimic the appearance, function, and/or feel of natural teeth;

Pulp capping: pulp capping is a dental procedure involving the application of specialized materials to the exposed dental pulp for protection;

Definition of "biomaterial"

Despite being conceptually easy to grasp, the consensus on the official, scientific definition of "biomaterial" presented many challenges and required various revisions over time [1]. A modern, widely accepted definition was coined during the "Consensus Conference" of Chester, UK in 1991:

> *"Any substance or combination of substances, other than drugs, synthetic or natural in origin, which can be used for any period of time, which augments or replaces partially or totally any tissue, organ or function of the body, in order to maintain or improve the quality of life of the individual."*

The use of a subjective parameter such as "quality of life" as part of a standardized definition has some major drawbacks, but it clearly reflects the importance that is nowadays given to the "subjective response" of the patient when compared to the brutal medical practices of just one century ago, when patients were often considered to be no more than an expendable testing subject. For these reasons, such a definition would be inadequate for an historical review, as "patient comfort" is a relatively modern concept.

To find a more adequate definition, it is necessary to look back to the year 1967 and consider what Dr. Jonathan Cohen, wrote [11]:

> *"There is no current agreement on what distinguishes biomaterials from others. For the purposes of this article, I will include all materials, excepting drugs and sutures, which are used as implants."*

As an orthopedic surgeon himself, Dr. Cohen was focusing his attention only on a limited range of potential applications and was far more interested in the materials' practical use than in comprehensive definitions. He proposed four categories of biomaterials: "metals," "bone and derivatives of bone used as grafts," "plastics" and "ceramics and composites".

Interestingly, by the time Dr. Cohen published the definition and classification in his essay "Biomaterials in orthopedic surgery," Dr. John M. Carnochan (1817–1887), Auguste S. Verneuil (1823–1895), Leopold Ollier (1830–1900), Vitezslav Chlumsky (1867–1943), William Steven Baer (1872–1931), Themistocles Glück (1853–1942) and many others physicians had already tested wood [1], soft tissues [12], adipose tissues [13], muscle tissue [14], pig bladder [15] and ivory [16] as a substitute material for articulations, meaning that many natural organic materials, not listed in the original four categories created by Cohen, were already considered—or at least tested as—potential biomaterials.

In the logic of Cohen, as well as for the purposes of this review, a material can be defined "biomaterial" only based on the results of previous clinical experiences, through a process of trial and error and this is exactly the same approach used by the pioneers of biomaterial science, researchers of the caliber of the already mentioned Chlumsky, but also Marius Smith-Petersen (1886–1953) [17], Arthur A. Zierold [18] and even the so-called "father of modern hip replacement," John Charnley (1911–1982).

On this review paper, we will mainly focus our attention on materials for dental applications. These materials face one of the harshest biological environments on earth: the oral cavity. Details on the mechanical, chemical biological and esthetical challenges faced will be given in the next section, but we must stress that, as stated in the 1982 definition, a material can be defined as "biomaterial" only in relation to its environment. Materials that can be applied in the orthopedic field are not automatically suitable also for dental applications, and vice versa. Moreover, different anatomical locations, even inside the same oral cavity, are subject to different *stimuli*, and the challenges faced increase exponentially as regards to pathological conditions, individual morphologies, personal habits, body size, age, sex, ethnicity, etc.

To put all these concepts into context, we can compare the short literature review from Palma Carrió et al. [19] to the retrospective study of Raikar et al. [20]. Despite implant morphology and size playing clear roles in the rate of failures, risk factors associated with early failure of dental implants are associated with age, sex, habits (smoking), implant location and bone quality/quantity. Even when these risk factors are not directly influencing the properties of the implanted biomaterial, they directly influence the chemical and mechanical loads it needs to withstand.

Even reliable biomaterials such as commercially pure titanium need to face adverse immunological interactions that result in alterations of the surrounding biological tissues [21]. These immunological interactions are also influenced by many factors, one of which seems to be related to age, with possibly younger patients rejecting implants more often than the elderly [22].

Additionally, patient specific conditions such as allergies can also drastically change the outcome of an otherwise perfectly biocompatible device: latex [23], nickel [24], amalgam [25], PMMA [25], cobalt [26] and even palladium [27] and titanium [28] are reported to occasionally cause allergic reactions when used in biomedical devices.

There is a major flaw common to all definitions of biomaterials: in order to be as general and omni comprehensive as possible, they end up ignoring all environmental conditions and other specific limitations which are actually key for the success of the devices. When looking at the archeological findings described in this review, the opposite is also sometimes true: in history, materials that should not be considered biocompatible could be used well enough—or for long enough—to be later found at their host's burial site. Moreover, since in historical times life expectancies were only a fraction of those of today and humans had priorities that were very different from the current ones, even a badly working implant that could last only three of four years might have had an overall positive impact on the life of its host.

Before digging further into the archeological literature, there is one last point we need to address: all definitions are misleadingly pointing to the biocompatibility of materials as a whole, while it is only the outermost layers of the surface that actually interact with the environment. Let us imagine a 10 mm diameter ball made entirely of pure titanium (I), implanted inside a larger bone: only the outermost layer of the sphere will be in contact with the biological environment and will be responsible for the outcome of the interaction. If we reduce the ball to a 1 mm thick hollow sphere (II), the only biologically relevant difference would be the elastic modulus of this peculiar implant, which would drop drastically. Now let's imaging filling up the hollow sphere with solid cadmium (III): this would compensate most of the drop in elastic modulus, making (I) and (III) virtually indistinguishable from a biological response point of view, despite cadmium being extremely toxic. With the exception of radioactive elements, we would be able to fill the hollow titanium sphere with most other metals on the periodic table without any noticeable change in its biological response. Now let's imagine progressively shrinking the thickness of the titanium layer: how far would we be able to go before the contents have a chance of touching the bone? The answer is, hypothetically, just a few perfect molecular layers.

This exercise might seem like an unrealistically simplified model to describe materials biocompatibility, but the presence of a nano-scale layer with a different composition is actually the only reason behind the biocompatibility of the full sphere (I) in the first place: metallic titanium never touches the bone, as it is covered by a spontaneously formed layer of titanium oxide (TiO_2), which is in turn covered by an even thinner layer of titanium hydroxide ($Ti(OH)_2$), and this nanometric ceramic bilayer protects the metallic titanium underneath from the oxidizing environment and, at the same time, it protects the environment from the harm that metallic titanium might potentially cause. The same protective film encases all biomedical grade titanium alloys, even the discussed nickel-titanium alloy known as Nitinol which, despite being generally considered safe [23], in very few occasions was responsible for allergic reactions to nickel [29].

Most biocompatible metals (titanium, cobalt alloys and stainless steel in particular) are covered by similar layers of protective oxides, but also polymers and even ceramics have, at their outermost surfaces, different properties and chemo-physical structures. Al_2O_3, for example, despite being one of the most chemically stable ceramics known to mankind, tends to form Al_2OH in water [30]. Perfect, nanometric (or even sub-nanometric) biocompatible layers would suffice in granting biocompatibility to most known materials but, due to their high energy, surfaces are always defective.

It is important to notice that even very successful surface-controlled deposition techniques, such as atomic layer deposition, fail at producing perfect layers [31]. Moreover, even initially non-defective films are doomed to eventually fail under mechanical or chemical stress. Still, unlike human-made coatings, spontaneously formed oxide layers possess self-healing capabilities.

The definition of "biomaterials," as we pointed out, possesses two main flaws and as a result can be misleading. A more phenomenologically accurate concept would be that of "compatible bio-interfaces," where the surrounding biological environment and the chemically altered outermost surface layer of the biomedical device are studied while coupled together.

The oral cavity

As mentioned previously, biocompatibility can only be addressed when the specific biological environment has been clearly defined, and even within the oral cavity the environment can be drastically altered by many external factors.

The simplest type of stress biomaterials face is mechanical. In the oral cavity, mastication is responsible for both compressive loads and abrasive wear at the interface between opposing teeth [32]. Despite mastication being modeled hundreds of times in the literature, anatomical variations and habits can radically influence the number of cycles, peak load and sliding forces dental biomaterials are subject to. Moreover, all these parameters change over time, making the final outcome somehow unpredictable. Biomaterials are designed with a significant safety margin, often capable of withstanding loads and stresses well beyond what is expected under normal conditions. This practice of overdesigning is rooted in the principle of ensuring the utmost safety for patients and users of medical devices or implants, but occasionally even the best designed biomaterials might encounter failure due

excessive wear, unexpected stress concentration or lack of stability.

The second stress biomaterials need to face is chemical. Despite saliva acting as a pH-buffering solution, the local conditions can be exacerbated by the presence of crevices, tartar or bacteria biofilm, leading to acidification. Moreover, food and drinks can temporarily alter the pH of the whole oral cavity, while specific ingredients, such as acetic and citric acid, can lead to teeth demineralization [33]. Chromogens can alter the appearance of teeth [34] while other molecules, such as nicotine, can cause various types of other damages [35]. Generally speaking, most substances we assume will interact with the oral cavity and bring some temporary alteration that, in particular conditions, can also become permanent [36].

Considering the microbial flora, the oral cavity is one of the most densely populated sites of the human body. As environmental conditions change from location to location, different microorganisms colonize different areas, and the microorganisms themselves then alter the surrounding environment. The asaccharolytic activity toward cysteine and methionine, for example, is responsible for oral malodor, while the activity of non-mutans *streptococci* and *actinomyces* on the supragingival ecosystem causes acidification, with consequent introduction of more cariogenic microorganisms and demineralization of the tooth surface. Overall, the oral cavity contains many species of bacteria, including *Actinomyces, Arachnia, Bacteroides, Bifidobacterium, Eubacterium, Fusobacterium, Lactobacillus, Leptotrichia, Peptococcus, Peptostreptococcus, Propionibacterium, Selenomonas, Treponema*, and *Veillonella* [37–39]. These microorganisms constantly interact with each other and with the environment, creating an incredibly complex microbiome. This might lead to changes in pH, inflammatory responses and oral pathologies that can drastically change the outcome of a medical treatment, as well as prevent the integration of the device with the surrounding tissues.

Successful biomaterials: a chain with three links

In the previous section, we pointed out that what really matters for biocompatibility is the outermost "skin" of a biomaterial, where the thickness of this layer depends on its capability to protect the material underneath from any contact with the environment.

The second key point for properly addressing biocompatibility is quite obviously the surrounding biological environment as it plays a crucial role on the mechanical and chemical stress this outside "skin" layer has to bear during its service in vivo. The more "aggressive" is the environment, the more "protective" (chemically, mechanically or even biologically) the skin has to be during its time in vivo.

And time is the third and last variable to control biocompatibility: all materials are doomed to fail over time, either catastrophically or by their progressive weakening, and only a very few are destined to outlast their hosts.

Aristotle said that "The whole is greater than the sum of its parts," but this is not the case for biomaterials, as they work as a chain instead: "a chain is only as strong as its weakest link" with the three links being surface chemistry, environmental stresses and minimum lifespan.

A chronological list of biomaterials reviewed in this article is presented in Table 1.

Ancient history

According to various literature references, the oldest dental prosthetic devices to ever see application were bamboo pegs, supposedly used in ancient China as a replacement for missing teeth. These claims, which were often the results of unverified tertiary sources, seem to be basically unsupported by scientific evidences as the primary sources are nowhere to be found or maybe lost in time [40].

Similarly, the older "bridges" in human history were associated with the highly developed Egyptian dentistry, but this statement again is not adequately supported by literature. While it is undoubtedly true that Egyptians were able to manufacture gold wires and that those wires were used to fix teeth into position, it is actually quite unlikely that they were ever actually used *ante mortem*.

The first finding of this kind, commonly known as the "Giza Bridge" [current location: Roemer—und Pelizaeus Museum, Hildesheim, Germany], dated back to the third millennium BC, was composed of two teeth, a lower second and a lower third molar, joined together by a piece of gold wire woven around the gingival margins. It was presented as an evidence for the oral healthcare advances of ancient Egyptians by Junker, back in 1938 [41] but it is nowadays considered controversial at least [6]. The device was most likely never intended for use *ante mortem*, and a possible simple explanation for the finding could be that it was inserted into the mummified corpse in an attempt to make the body whole again and ready for the afterlife, a practice which was common in ancient Egypt. In a recent critical review concerning the osteological evidences for dental therapy in Ancient Egypt, the authors concluded that only four of the eight osteological examples described in literature, which included among others the Giza Bridge, can be can plausibly attributed to ancient Egyptian interventive dental therapy: the Tura el-Asmant bridge that will be discussed later in this section, one enucleation, a lesion filling and a filling [42].

Table 1 chronological list of the materials presented in this review, along with location, year of use (estimated when not directly available), application, remarks and literature references

Material	Location	Time	Application	Remarks	Refs.
Bamboo	China	3000s BC	Dental pegs	Unconfirmed	[38]
Gold	Egypt	2500s BC	Supports (wire)	Contested	[6, 39]
Ivory	Egypt	2000s BC	False teeth	Contested	[40, 41]
Copper	Egypt	–	Dental pegs	*Post mortem* Not biocompatible	[42]
Bone	Etruscan	500s BC	False teeth	–	[43, 44]
Ivory	Etruscan	500s BC	False teeth	–	[43, 44]
Gold	Etruscan	500s BC	Supports (bands)	Bioinert	[43, 44]
Gold	Phoenician	300s BC	Supports (wire)	Lack of information Unknown scope	[45]
Teeth	Phoenician	300s BC	Transplants?		
Iron	Gaul	250s BC	Dental pin	*Ante* or *post mortem?* Not biocompatible	[46]
Iron	Gaul	100s AD	False teeth	Contested	[47, 48]
Shells	Maya	600s AD	False teeth	Biocompatible	[49]
Minerals	Maya	600s AD	Esthetic inlays	Various mineral stones, mainly bio-inert	[50]
Amalgam	China	659s AD	Fillings	–	[51]
Stone	Maya	800s AD	False teeth	Probably serpentine Bio-inert or slightly bioactive	[3]
Gold	Atacames	–	Esthetic inlays	Bio-inert	[52]
Teeth	Atacames	–	Transplant	Successful	[52]
Wood	Japan	800s AD	Dentures	–	[53]
Gold	Italy	1400s AD	Fillings	Hammered foils bio-inert	[54]
Teeth	France	1500s AD	Transplant	Successful	[55]
CuHg	Germany	1659 AD	Fillings?	–	
Lead	France	1700s AD	Fillings	–	[56]
Tin	France	1700s AD	Fillings	Biocompatible Easily replaced	[56]
Copper	Germany	1700s AD	Fillings	Not biocompatible	[57]
Silver	Germany	1700s AD	Fillings	Not biocompatible	[57]
Gold	Germany	1700s AD	Capping	Used to save dental pulp	[57]
Porcelain	France	1700s AD	Dentures	Bio-inert	[58]
Platinum	Italy	1700s AD	Dental pins	Bio-inert	[59]
Lead	US	1790s AD	Denture bases	Toxic	[60]
Porcelain	US	1800s AD	Dentures	Bio-inert	[61]
Porcelain Platinum	England	1800s AD	Dental implants	Bio-inert	[62]
PbBiSn	France	1800s AD	Fillings	Painful when applied	[51]
PbBiSnHg	France	1818 AD	Fillings	Lowered melting point	[51]
AgHg	France	1800s AD	Fillings	Just needed annealing	[51]
AgHg	England	1819 AD	Fillings	From filed silver coins	[51]
AgHgZnCuSn	US	1896 AD	Fillings	Stable and strong	[63]
Gutta-percha*	US	1800s AD	Fillings	Bad aesthetics	[64]
Rubber*	US	1851 AD	Denture bases	Stable over time	[65]
Celluloid*	England	1869 AD	Denture bases	Not stable over time	[66]
Sandarac*	?	1800s AD	Bond/sealant	–	[67]
Cheoplastic	US	1800s AD	Denture bases	Easily corroded	[68]
Rose pearl*	US	1860s AD	Denture bases	Also nitrocellulose	[69]
Bakelite*	US	1924 AD	Denture bases	Bad aftertaste Poor shelf life	[70]

Table 1 (continued)

Material	Location	Time	Application	Remarks	Refs.
PVC*	US	1930 AD	Denture bases	High stability Formed fissures	[71]
PMMA*	US	1937 AD	Denture bases	Degradation in vivo	[72]
PMMA*	US	1900s AD	Restorations	–	[73]
PMMA*	US	1900s AD	False teeth	–	[73]
Plastupalat*	Germany	1900s AD	Denture bases	–	[74]
Stainless steel	US	1900s AD	Orthodontics	High strength Low costs	[75]
Stellite	US	1900s AD	Orthodontics	High strength Low costs	[76]
Vitallium	US	1932 AD	Orthodontics	As stellite	[77]
Vitallium	US	1930s AD	Screws	As stellite	[78]

Materials marked with "*" are polymeric and thus prone to similar degradation mechanisms over time in vivo

Fig. 1 El-Quatta bridge (Courtesy of the Egyptian Museum, Cairo)

A second appliance (Fig. 1), similarly dated back to about 2500 BC, was excavated at el-Quatta, near Cairo [43] [last known location: Museum of Egyptian Antiquities, Cairo, Egypt]. Before discussing the nature of such a finding, it is necessary to observe that the prosthetic restoration was not found in situ (in the oral cavity of the corpse) but among the crushed bones of a skull. This means that there is no actual proof that the metal was actually ever applied in vivo to begin with. The most accredited hypothesis in recent literature is that the teeth were removed accidentally during life or dislodged during the mummification process and then reunited with the other remains of the skull *post mortem*.

One final Egyptian gold appliance was found in Tura el-Asmant (Fig. 2), this time attached to the teeth of the skull and may have been in use for some time [current location: Department of Antiquities, Cairo, Egypt]. Unlikely the previous reports, this implant (or prosthetic restoration, opinion is still divided on this matter [42]) was dated to a much latter period (Greek Ptolemaic), about 332–330 BC. At that time, trade and cultural exchanges were common in the Mediterranean area and it is likely that the technique was actually imported from other cultures, as it resembles dental works found in Sidon (Greece) or Etruria (Italy) [6].

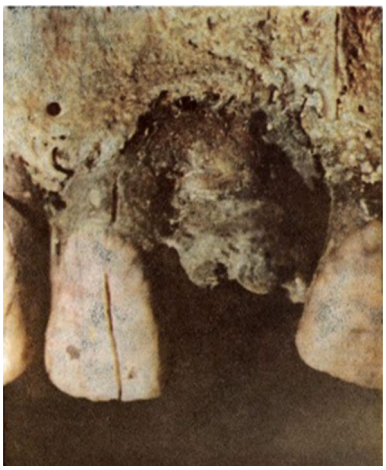

Fig. 2 The Tura el-Asmant Bridge. Labial view of the fractured right maxillary central incisor within its socket. Reprinted with permission from Ref. [42]

These findings support the hypothesis that the ancient Egyptians were one of the first cultures to insert gold wire around teeth, but the technique, initially used only on corpses, was extended to dental appliances only after it was re-introduced from other countries.

Another, unsupported Egyptian primacy in dentistry is the use of ivory to produce false teeth [44]. In this case, all literature references are based on a series of spurious samples [45], and, as Frank Filce Leek—an authority on ancient Egyptian dental disease and treatment—stated, there were probably no professional doctors able to apply prosthetic implants to living patients at the time [46].

One last, famous spurious sample from ancient Egypt is the copper peg found inserted into an upper jawbone [47], but again the prosthetic implant seems to have been placed *post mortem* for aesthetic purposes.

By the sixth century BC the Etruscans, living in the central area of Italy, were actually the only producers of false teeth for prosthetic replacement in the region, using either bone or ivory [48]. Etruscan prosthetic teeth, which were originally found only on women, used gold wires (or even bands) to fix the devices into position. The lack of anterior teeth, particularly common on Etruscan women, was often as a consequence of dental evulsion [49].

The simplest Etruscan prosthetic replacements were gold band dental bridges like the two acquired by William C. Barrett [current location: unknown]: both bands were probably worn in the upper jaw of woman, enclosing respectively three and four of her maxillary incisors [49]. A similar device, this time formed by three cold-welded gold rings and holding a prosthetic replacement in the central position, was found in the late nineteenth century on lake Valseno, not far from Rome, but has since disappeared. From the illustrations we possess, it appears that the replacement tooth was held in position like a gemstone. Another similar device, known as the "Copenhagen prosthesis," is currently at the Danish National Museum. Unlike the other appliances, this device could be dated back to 500–490 BC. Again the Copenhagen bridge is made of three separate rings cold-welded together. The left loop is fitted to the upper left central incisor, and the loop on the other end had been fitted to the right lateral incisor. These teeth served as the anchor or abutments, those sound or living teeth to which the bridge was attached to hold it in place. The rectangular central loop held a false (ivory or bone) tooth [49].

The Satricum prosthesis (Fig. 3), another Etruscan prosthetic replacement [current location: Villa Giulia Museum, Rome, Italy], features also a golden capsule onto which the classic encircling strip is attached and a remodeled natural tooth, probably in order to remove a cavity [50]. Another two devices, the Palestrina and the Falerii Veteres prosthesis, both make use of pins for the solid reinforcement of teeth, with the latter being more elaborate in its design. It should be noted that, unlike most previous devices, the prosthesis of Falerii Veteres was most likely used by a male host.

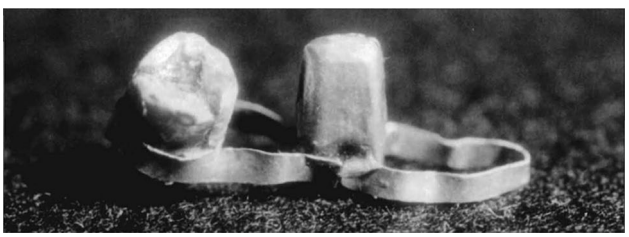

Fig. 3 Satricum prosthesis, reprinted with permission from Ref. [50]

A similar, later device (Fig. 4) [last known location: National Museum of Beirut] was also found by Dr. Gaillardt during an excavation expedition at the Phoenician necropolis of Sidon: "A superior[sic] jaw of a woman showing two canines and the four incisors united by a gold wire[…] Two of these incisors seemed to have belonged to another person and to have been inserted there in order to replace those which were missing." [52]. Even if these findings were successively reported by many other authors, crucial details about the origin and scope of the Sidon prosthesis, an almost unique example of Phoenician dental aesthetic devices, are still unknown. It must be noted that the Etruscan findings predate the Sidon's Phoenician device and the Tura el-Asmant Egyptian device by at least two centuries, suggesting that the Etruscan craftsmanship knowledge spread across the Mediterranean area.

The common thread between all these early devices is the use of gold for fixing the replacement tooth to the surrounding teeth, or even as a capsule. If we have a look further back in time to about 3000 BC, we will find that even the oldest prosthetic device known to man, an artificial eye made of natural tar which was found in Iran, was covered by a thin layer of gold [1], making gold de facto the oldest biomaterial to be successfully applied *ante mortem*. Most sources point out that gold, apart from being easily molded into a desirable shape, is biocompatible because it is not toxic and it doesn't rust [53]. In the first section of this paper we mentioned that the definition of biomaterial should be based purely on the surface interactions but gold, being a noble metal, does not react with the surrounding biological environment. Low-gold alloys do tend to tarnish over time [54], but high-gold alloys are basically ignored, making gold one of the few—if not the only—really bio-inert material [55] that somehow defy our previous definition.

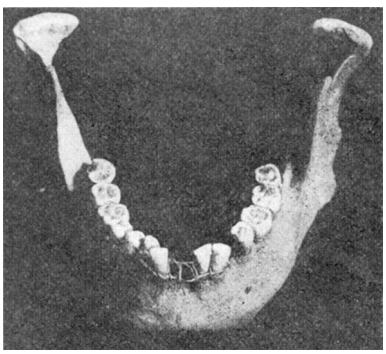

Fig. 4 prosthesis from the necropolis of Sidon, reprinted with permission from Ref. [51]

The gold alloys used by Egyptians for producing jewelry and ornaments usually contained relevant amounts of silver and copper [56]. We now know that percentages of silver close to 50% would make gold alloys cytotoxic and thus unsuitable for internal applications, but most devices were made with at least 80% of gold, resulting in an alloy that would be considered biocompatible even for the standards of the twentieth century [57, 58]. Various pre-Columbian cultures in South America, such as the Inca, Moche, and Chavín civilizations, worked with gold to create intricate jewelry, ornaments, and artifacts. They used various techniques to extract and process gold from natural sources like rivers and streams. The gold naturally contained varying amounts of other metals and minerals, such as copper, silver, and iron but, after processing, these reached relatively low concentrations [59] that would not compromise the biocompatibility. Etruscan possessed the metallurgical skills necessary to purify gold [60], but for dental applications often used an alloy containing 65–75% of gold, 22–35% of silver and 0.5–3% of copper, very flexible and easy to mold [61] that would be not biocompatible following modern standards. Phoenicians, on the other hand, did make use of relatively "low gold" alloys with silver content up to about 50% [62], that would not be considered biocompatible by modern standards.

The Phoenician dental appliance found at Sidon utilized the individual's own teeth, which had previously been lost or deliberatively removed, as part of the restoration. Other materials used at the time involved carved bone, ivory or animal teeth.

There are a few references of dental transplants during the "Classic Age," in particular by Roman and Greek scholars: the physician Hippocrates, considered by many one of the most outstanding figures in the history of medicine, mentioned the use of silk threads and gold wires to anchor teeth to the gums, while the encyclopaedist Aulus Cornelius Celsus in his treaty "De Medicina" mentioned the possibility to replace missing teeth with equivalent elements taken from cadavers [63]. We do not have any statistical sources for the actual use of dental transplants during the Classic Age, nor we do have reliable information about the outcomes of such procedures, but these two references, further supported by many other "minor" authors of the time, prove just how developed these two cultures were at their peak. It took almost two millennia for dental transplants to be mentioned again in literature in the researches of the French physician Ambroise Paré and the father of modern dentistry, Pierre Fauchard (sixteenth and seventeenth century) until eventually becoming a common practice for early American dentists (Baum and Hertz [64]).

Despite the early successes, no reliable, scientific record of bone or teeth transplants exists either in literature or in archeological findings from the time of Celsus to the sixteenth century, an outstanding gap of more than 15 centuries.

Silk ligatures, not dissimilar in form or composition from the ones mentioned by Hippocrates, were used over the centuries to fix teeth position [65]. Silk is still investigated nowadays as a promising biocompatible material with high strength-weight ratio [66]. Despite being considered overall biocompatible, silk and silk-based materials were recently found to cause pro-inflammatory immunogenic responses as exhibited by the high levels of pro-inflammatory cytokines [67].

The La Tène Celtic Gaul burial site at Le Chêne in northern France is the location of another peculiar, almost unique finding. Numerous metal objects, including bronze torcs, anklets and bracelets, fibulae and belt rings, and coral and amber bead necklaces, recovered from these burials place them in the Late Iron Age (300–250 BC) [68]. At the burial, an iron pin was discovered in place of an upper incisor in the mouth of a young Celt woman [current location: unknown]. The pin itself appears to be heavily corroded by the acidity of the soil, a fate it shared with the enamel of the natural teeth. While the loss of a central incisor does not carry any major consequences for mastication, it may have had important attendant aesthetic or phonetic repercussions. The replacement of a missing tooth may be in keeping with the maintenance of appearances in a civilized society [69]. As there is no actual proof the pin was actually *ante mortem*, archeologists proposed three possible alternative hypotheses: an intra-radicular *ante mortem* insertion, an attempt at intra-socket *ante mortem* insertion or a *post mortem* ornament. Only the second of these three hypotheses would require the pin to actually be biocompatible.

First of all, the "iron" pin is actually not made of what we call iron. Iron does not occur naturally and most of the metallic iron in existence is actually steel, as it contains relevant amounts of carbon. Further information on the chemical composition of the artifact were not published, but considering the geographical location it can be assumed it to be at least comparable with the iron produced at Puisaye or Sénonais-Pays-d'Othe, which would also be in line with the dating of the burial site. Both sites produced a slag poor in MnO, K_2O and P_2O_5, with unusually high traces of Cerium and Yttrium [70]. Unlike stainless steel, carbon steel is not considered to be a biocompatible as it rapidly corrodes in vivo. Nevertheless, iron oxides are nowadays commonly used for the production of biocompatible nanoparticles for various medical applications [71]. Again, what really

matters for biocompatibility is chemical composition of the outermost layer of the device, which we can assume to be based on iron oxides, in combination with the surrounding biological environment. According to the Pourbaix diagram for iron, a layer of stable Fe_3O_4 phase can only be formed in alkaline environments, but this is only true for its metallic form. In reality we do not know how thick and stable the oxide layer was when the pin was first applied. Moreover, we do not have enough information on the medical procedure and the lack of sterile conditions could easily have provoked an unfavorable host response. From what we know, it is unlikely but not completely impossible for the implant to be inserted *ante mortem*. The unusually high amounts of Cerium [72] and Yttrium [73], both elements that we nowadays know to be bioactive and able to promote osteointegration, might also have played a minor role in the positive outcome, but we simply lack the necessary information to make a based claim.

The first half millennium AD

The oldest recorded proper dental implant (Fig. 5) was discovered on the body of a Mayan woman who dated back to about 600 AD [74] [current location: Peabody Museum of Archaeology and Ethnology at Harvard University, United States]. It consisted of two seashells which were placed into existing tooth sockets. Despite being often used as evidence for a long-forgotten but once common practice, to date no other implants of this kind were ever found. The implant might as well be one of a kind, considering all the complications that could arise from xenotransplantation at a time when not only pathogenic infections but also immunological reactions were far from being understood.

Since the time it was excavated, back in 1931, scientists simply assumed that the teeth implants were just inserted *post-mortem* in order to restore the original integrity of the body. It was only in 1970 that the skull was analyzed in higher detail, leading to the discovery of human bone tissue formed on the external surface of the xeno-transplant in vivo, meaning that the host was not only alive at the time of implantation but also that the implant was not rejected and was instead successfully osteo-integrated over time.

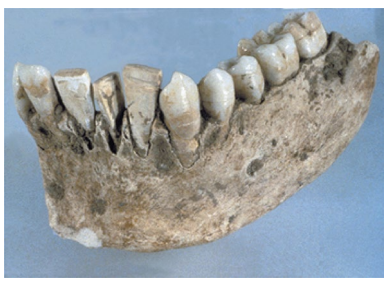

Fig. 5 Mayan seashell implanted false teeth, curtesy of the Peabody Museum of Archaeology and Ethnology at Harvard University

From this point of view, this peculiar marine xeno-transplant might also be the earliest proof of bioactivity for calcium carbonate, the main constituent of seashells [75]. However, calcium carbonate only accounts for 70–95% of the total mass, with the remaining 5–30% including not just other minerals, such as SiO_2, but also organic matrix, in particular proteins and glycoproteins [76]. Moreover, seashells are often colonized by various sclerobionts (organisms living in or on hard substrates) such as *bryozoa*, *porifera*, *retaria* or other *mollusca*, most of which are also planktonic species (tychoplanktonic in particular) [77]. Shellfish can also be contaminated with various kinds of dangerous biotoxins [78] and even if we do not know how the seashell was prepared and cleaned at the time, it still represents a potentially life threatening bio-hazard. Moreover, the small organic fraction contained in the seashell can also trigger a strong immunological response leading to implant rejection.

The fact that the implant was covered by bone tissue indicates that it could be osteo-integrated in vivo, over time. This is an outstanding achievement considering that it predates any study on osteoinduction, osteoconduction or, more in general, bioactive materials.

Calcium carbonate is one of the two most common bio-minerals, but while commonly found in shells and eggs, it is not the main constituent of bones or teeth, which are instead based on calcium phosphate (in the form of hydroxyapatite) [79]. However, calcium carbonate can be used as a bone substitution material and it can even take part in bone remodeling [80], meaning that it can be resorbed and converted into mature remodeled bone. The transmembrane proton pumps in osteoclast cells that are responsible for lowering the pH sufficiently to dissolve both calcium phosphates and carbonates [81], meaning that the two calcium based bio-minerals are interchangeable, up to a certain extent.

Natural calcium carbonate sources, coral [82] and mussels [83] in particular, are still used today to produce bone substitution materials, often after being partially converted in apatite using hydrothermal replacement processes [84]. It is surprising that the same biomedical technology used by the Mayan civilization and long forgotten has resurfaced centuries later and established itself as a competitive alternative to more complex, man-made modern bone substitute materials.

Another Mayan contribution to the field of dentistry that made its way up to the twenty-first century are aesthetic modifications. An investigation of the ancient Mayan burial site called “Midnight Terror Cave” found

102 (out of 337) aesthetically modified incisor teeth [85]. Midnight Terror Cave is a Late Classic period (550–900 AD) burial site situated in Belize, and it is believed that most of the 10,000+ skeletal elements are derived from sacrifice, given signs of trauma on bone, the archeological context and subadult demographics [86]. Now, teeth carvings have no direct connection with biomaterial science, but Mayan modifications were not limited to that: upper-class Mayans often also perforated their teeth in order to enchase mineral stones. Micro-CT scans from six well-preserved teeth from Mayan corpses found in an archaeological site in Guatemala (about 1600 years old) showed that these perforations often reached the pulp chamber, resulting in inflammatory resorption or partial calcification of the cavity [87].

Mayan dental modifications followed a list of preferred "styles" that were meticulously collected and catalogued in nine main types by Javier Romero Molina [88]. There is no evidence that dental filing or inlay insertion was therapeutic; rather, it is believed to have been done for ritual or aesthetic purposes as the modified teeth were not likely actively used in mastication [89]. The inlay stones were held into position using a mixture which is considered to be chemically comparable to the Portland cement used in constructions [90]. The types of stones used for inlays varied both geographically and temporally but included pyrite (FeS_2), jade (jadeite sub-type, $NaAlSi_2O_6$), turquoise ($CuAl_6(PO_4)4(OH)_8{\cdot}4H_2O$), hematite ($Fe_2O_3$), and obsidian (a mix of SiO_2, MgO and Fe_2O_3) [90]. It must be noted that reference [90] mentions both "jade" and "jadeite" in the list of inlays, as separate minerals, probably referring to "jade nephrite" simply as "jade". Despite the presence of limited nephrite deposits in the Motagua river's valley, Mayan artisans in reality had little interest in this mineral [91] and colloquially 'jade' objects in Mesoamerica are composed of jadeite. Another possibility is that the document refers to similar relatively hard greenstones such as albitite $Na(AlSi_3O_8)$, omphacite ($(Ca,Na)(Mg,Fe^{2+},Al)Si_2O_6$), chrysoprase ($SiO_2$) or quartzite ($SiO_2$). The exact composition of these gems would be important in order to properly address their biocompatibility in the oral cavity, especially considering that they come in direct contact with the pulp chamber, which does not possess any additional protective encasing. While SiO_2-based gems are probably biocompatible and stable over time, for example, albitite and jadeite will slowly dissolve in both alkaline and acidic environments [92, 93].

But seashell-based false teeth and esthetic modifications were not the only Mayan contributions to the field of dentistry: further excavations in Copan, Honduras uncovered the skull of a young women dated around 800 AD [current location: unknown]. The skull (Fig. 6) presented maxillary teeth carved and decorated with colorful stones as well as a carved stone replacing one of the mandibular anterior teeth [3]. We already discussed the Mayan practice to modify the esthetics of teeth using stone in the previous paragraphs, but the stone teeth might also have served a different function [94], as also observed by Dr. Andrews, one of the most well-known dental archeology authorities: "In the lower jaw of the skeleton was found the most interesting curiosity in the whole collection to dentists—a lower left lateral incisor that has been carved from some dark stone, and which has been implanted to take the place of one that has been lost." At the time, Copan was a major Mayan city at the peak of its height so it is not surprising that it was also the location of such a finding, yet the most unique Mayan stone dental prosthetic was found in the cosmopolitan city of Tlailotlacan [95]: one incisor in her lower jaw was replaced with a prosthetic made of serpentine, a green stone carved in the shape of a tooth (Fig. 6) [current location: National Anthropology and History Institute, Ciudad de Mexico, Mexico]. Both findings show signs of tartar and abrasion wear, it has been speculated that they have been used for at least a few years. Serpentine stones have many polymorphic phases, but with chemical composition similar to $Mg_3Si_2O_5(OH)_4$. One of the most common minerals in this group, chrysotile (white asbestos) despite being toxic when inhaled [96], has been proposed as a bioactive filler material for tissue engineering applications thanks to its low cytotoxicity when implanted [97]. The relative bioactivity of serpentine minerals might be caused by the leaching of $Mg(OH)_2$,

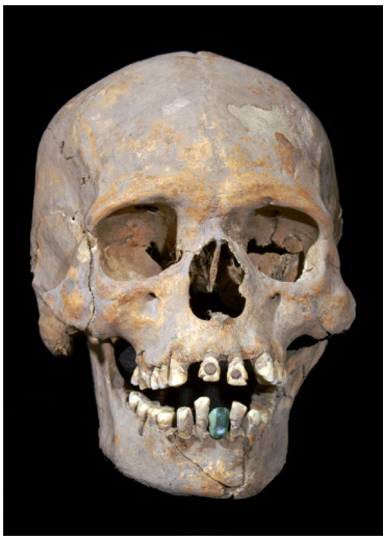

Fig. 6 Skull with serpentine teeth. Curtesy of the National Anthropology and History Institute, Ciudad de Mexico, Mexico

a mechanism similar to that of bio-resorbable magnesium alloys still studied nowadays [98].

While stone fillings were relatively common in Mexico and Central America, in the Ecuadorian city of Atacames, not far from Esmeraldas, skulls with tiny discs of gold set into the teeth in the same manner (with the exception of the material) were found in various burials [99]. Three similar findings from the areas surrounding Esmeraldas are displayed at the British and Heye museums: a skull with eight small inlays of gold on various teeth, the maxilla of a skull with two gold thin discs in cavities bored into the enamel and a skeleton with four incisors and two canines of the upper jaw decorated with gold inlays. Another interesting device discovered in the same region is a wire interlaced between the teeth of a skeleton that was found to be purely esthetical [100].

Gold has been used in South America since at least 2000–1500 BC, even though there is no proof that gold was chosen for its intrinsic antiseptic properties or for its high biocompatibility: Incas, for example, used gold to produce a wide array of different objects, going from accessories to utensils and even surgical blades [101]. The use of gold is one of the possible explanations for the exceptional success rate of cranial surgery in the pre-Colombian era, but its preference over other materials was probably driven by two key aspects: the high workability, and the spiritual meaning associated with its brilliance and resistance to oxidation [1], which is also the reason behind its biocompatibility, as observed in the previous section: gold is stable over time and its surface doesn't interact with the surrounding biological environment [102].

Even if gold was indubitably the most common biomaterial at the time, there is one more metallic finding from this era worth mentioning. Again it is (or at least it appears to be, as we will see later) an iron tooth implant from a Gallo-Roman necropolis at Chantambre (Essonne, France) [103] [current location: Le Musée Intercommunal D'Etampes, Etampes, France], not far from where the iron pin from the previous section was found. Unlike the previous case, this dental implant was applied *ante mortem* and achieved a relatively good level of osteointegration with the surrounding bone tissue. The individual in question, a man who was over 30 years old when he died, is dated to the end of the first century or beginning of the second century AD. Despite being severely corroded; the implant appears to be made of low-alloyed steel with traces of silicon (0.73%) and calcium (0.26%). It was likely to have been inserted by impaction soon after the tooth loss and even if chance surely played a major role in this success—if proven authentic—would constitute proof that iron-based prosthetic devices are indeed feasible. The authors of the study [103] claim that the rugged surface of the prosthesis might have also contributed to the adhesion [104], but in the end, due to the lack of similar findings, it is nowadays impossible to estimate the survival rate of such an operation. We should also keep in mind that the average life-span was much shorter at the time, and even only 1 year spent in vivo constitutes an exceptional success for an implant.

There is one last Pre-Colombian archeo-implant finding worth mentioning in this paragraph: the very same maxilla of a skull with two gold thin discs mentioned in the previous paragraphs also has another unusual dental feat in the right central incisor. It is indeed not a right central incisor, but a right lateral incisor which does not belong to the jaw but was implanted to replace the central incisor. The tooth fits perfectly into the socket, although, as a matter of course, it is not so long as the cavity, this space at the end being proof that the original tooth was replaced by the implanted one only a short time before death, otherwise the growth of the bone would have filled it.

A few literature references date back teeth transplants to ancient Egypt, going as far as mentioning slaves being forced to give their teeth to the pharaoh, but it must be noted that the original document all these references point to, "History of Dentistry" by Dr. Vincenzo Guerini, does not make any mention of such a practice or even of tooth transplants to have ever occurred in ancient Egypt [105], making the Mayan finding the oldest confirmed case of successful tooth transplant.

Becker [106], an authority on ancient dental appliances, hypothesized that the Chantambre specimen could be a natural tooth stained with iron oxides, and not an iron implant, and suggested that more tests are necessary to prove the authenticity of the finding. The original authors of the paper then pointed out that metallurgical analysis were indeed performed on the finding [107] and added that the absence of aseptic conditions does not systematically imply the rejection of the implant. While the scientific disagreement is of little use to us, the last sentence has a crucial importance in the interpretation of biomedical findings: what we see is just what survived. We do not know how many iron teeth failed due to aseptic loosening for each one that could succeed. It could be one in ten as well as one in a million.

The dark age(s) of dentistry

As previously mentioned, there were very few medical advances made during the Middle Ages. Most reviews on the history of medicine and dentistry skip one full millennium noting that it was a dark time for science in general. But depending on the geographical location, the lack of technological advancement in dentistry started at a different point in time, lasting for longer or shorter periods.

In Europe, the lack of innovation in dentistry extended up to the beginning of the eighteenth century and is often referred to as "The Dark Age of Dentistry" [108].

Even the darkest of ages saw a few, bright lights. One of these is certainly Johanues Arculanus (1390–1458 AD), professor of medicine and surgery in Bologna and, afterwards, in Padua. Arculanus developed what is now known as "dental filling," using leaves of gold carefully hammered on the cavities [109]. During the European Middle Ages we also saw the decline of the Mayan civilization [110] where tooth stone inlays progressively less common in favor of tooth filing [111] during the Late Classic (700–900 AD) and Post-classic (1000–1500 AD) periods [112].

The Middle Ages also mark the decline of the Gupta Empire in India, followed by the Muslim conquest of the subcontinent and the decline of Buddhism and ultimately the creation of the Bengal Sultanate. Dentistry in some form had been practiced since the era of the Indus valley civilization. However, since about 600 BC Indians made use of Ayurveda remedies for most of the problems related to the oral cavity, and no conspicuous technological advancement has be made in the subcontinent until the nineteenth century [113].

"Medieval China" stands for the period in Chinese history between the fall of the Han dynasty (220 AD) and the fall of the Mongol dynasty (1368 AD) and unlike its European counterpart is generally considered to be a period of technological evolution in all fields. The first mention of dental amalgams dates back to 659 AD, predating Arculanus by almost 800 years, and it was composed of 100 parts of mercury, 45 parts of silver and 900 parts of tin [114]. Despite its early invention, the Chinese amalgam will be discussed in detail in section From 1500 to 1900 AD, among its more modern equivalents. It is also well documented that the Chinese developed the first bristle tooth brush during this period [115]. However, Chinese dentistry relied predominately on oral remedies and traditional medicine and the first dental school was established only at the beginning of the twentieth century [116].

With the noticeable exception of wooden dentures [117], Japan does not have a proper history of dentistry and orthodontics up until very recent times. The country historically resisted outside influences and frequently closed itself off to foreigners and it was only in 1853 when Commodore Perry sailed his fleet into Tokyo Bay forcibly opening Japan to foreign markets. Western medicine and science were introduced in 1868 when the new Meiji government took office; however, dental education was neglected by the new regime. Japanese dental education originated in the private sector, when Dr. Kisai Takayama recognized the need and established the Tokyo Dental College, the first dental school in Japan, in the late nineteenth century [118].

Japanese wooden dentures date back to the eighth century: the wood used to make these prosthetics was usually a local type of plum tree, very hard and close grained. The teeth used varied from real human teeth to ivory or stone imitations. To improve the aesthetics of the prosthetic device, multiple teeth were usually carved from the same block, so that the plate and teeth were in one piece [119].

Wood is a composite material containing cellulose, hemicelluloses, lignin, and extractives and assessing the biocompatibility of such a complex system can be extremely challenging. Moreover, wood is harvested from biological organisms that can in turn host pathogens and parasites that can be lethal if transmitted to human beings. Wood wear can produce dangerous splinters that can easily penetrate soft tissues. Although the topic has garnered significant scientific interest in the past [120] and despite wood possessing high mechanical strength-to-weight ratio, durability and potential biocompatibility, in modern dental practice wood has been completely put aside in favor of polymeric and ceramic materials, which are easier to sterilize and more stable over time.

Many other countries around the world do not possess an ancient record of their own developments in the fields of dentistry and orthodontics, and if advances were made before the sixteenth century they probably did not find widespread application, as no record of the findings survived until today. Still, we do know that dentists around the world at the time were able to practice resection (the surgical removal of part of the tooth or the surrounding tissue), extraction and filing of teeth [121].

From 1500 to 1900 AD

Ambroise Paré (1510–1590) is considered to be the father of modern surgery, as he developed new, more successful tools and procedures. This is especially surprising considering he was a barber surgeon, a medical professional figure from the middle ages which, unlike trained physicians, could perform surgeries but had a more basic knowledge of the functions of the human body.

Paré's most famous innovations in surgery and orthopedics will not be discussed here, as we will focus only on his discoveries in dentistry. He described proper methods for extracting teeth and incising of the gums to help a tooth erupt. He also endorsed replacement of missing teeth with implants made of bone and ivory.

He has one of the best and earliest written case reports of successful tooth transplantation: a princess had a maxillary central incisor tooth extracted, so, a tooth was taken from one of her maids, and placed into her socket [122]. After some healing time, she was

able to use this new tooth with ease and just as well as if it was her own. With Paré, teeth transplants became a common practice in Europe that lasted at least until the early 1800's. As consumer culture gathered momentum, dentists went out hunting teeth, extracting them from corpses, or even going as far as buying them by the barrel from battlefields [123]. In the late nineteenth century, the dentures that were made with the teeth of the soldiers that died in the Battle of Waterloo came to be known as "Waterloo teeth." One last contribution of Paré was in the treatment of caries: he developed a cauterization process with acid to stop the progression of the cavity, but he never mentioned the application of fillings.

Between the various materials that can be used to replace a missing tooth, an analogous tooth would be the most obvious choice. Still, despite the various attempts at auto- and xeno- (heterogeneous) transplantation, the success of the transplantation procedure was anything but obvious. The idea of tooth transplant "rejection," or even the conditions for its "acceptance," are based on a very limited number of animal and human studies that lead to the actual skepticism and prejudice towards these procedures. There are basically three types of transplantation, either autogenous (from one site to another in the same individual), homogenous (form one individual to another of the same species) or heterogeneous (from one species to another species) and all three categories have an history of successes and failures. A review reporting a total of more than 2000 cases [124] showed resorption 5 years in only 26% of the cases and usually for teeth that remained out of the mouth for long periods after evulsion. Autogenous transplantations were overall more successful than homogenous, with heterogeneous being the more prone to immune-responses [125].

After Paré it was Pierre Fauchard (1678–1761) who further developed the modern practice of dentistry. As his predecessor, in a significant break with the tradition of the time, Fauchard shared his knowledge and techniques with colleagues, also publishing dental textbooks, in particular the text "Le Chriurgien Dentiste ou Traité des Dents" (translated as "The Surgeon Dentist or Treatise on the Teeth") [126].

Pierre Fauchard described the anatomy of teeth, instruments and techniques and pointed out that sugar (and not tooth worms, as previously believed) was responsible for caries. Moreover, he was the first clinician to suggest the use of dental fillings with lead, gold and tin foil [127]. He described dental bridgework and crowns with principles that are still accepted today and he also introduced new and innovative designs for the obturators (specialized prosthetic devices used to close or block openings in the palate) that were first described by Paré.

Few examples of tin dental fillings have survived, the most noticeable being the remains of an individual buried in Saint Maurand's Chapel of Saint Amé and dated between 1698 and 1776 [128] [current location: Collegiate Church Saint-Amé, Douai, France]. Due to its resilience, tin foil could be used on teeth where non-adhesive gold foil could not. When tin wore down, it could be replaced inexpensively, easily, and rapidly, a practice that would be unthinkable of in modern days.

The release of metal ions and wear debris from dental and orthopedic devices directly affects their biocompatibility, but it is confirmed in literature that tin, either in form of bulk or in powders, is generally biocompatible [129]. In biological pH, tin forms a surface layer of SnO_2 which is fairly resistant to corrosion [130]. Sulphide solutions, sulphurous acid and some foodstuffs containing organic sulphur compounds, produce stains of sulphide, but the corrosion rate is relatively low. When compared to SnO_2, PbO is stable in a wider range of pH, which would make it a better candidate for biomedical applications. Nevertheless, the dangers related to the exposure to lead have been known for centuries. Lead and lead oxides are cytotoxic [131] and at high levels of exposure lead attacks the brain and central nervous system, causing coma, convulsions and even death [132]. The reason why lead was still used at that time, despite the knowledge of its toxicity, was related to the lack of alternatives and the limited amount of ionic release over time, which was considered acceptable.

The German dentist Phillip Pfaff (1715–1767) was the author of "Abhandlung von den Zähnen des menschlichen Körper," translated as "Treatise on The Teeth of the Human Body and Their Diseases," the first German textbook on dentistry. He is responsible for many advances in the practice, going from the use of dental and arch impressions [133], to the introduction of new materials for artificial teeth, silver and copper in particular. He is known for being the first to successfully perform pulp capping with gold leaf before placing a filling, in opposition to the principles of the time which considered an exposed pulp as impossible to save [134].

Today, we know that both silver and copper are, in most cases, good antibacterial agents but "bad" biomaterials due to their relatively high cytotoxicity [135]. In reality, as for most materials, the biocompatibility of both metals depends on the anatomical location, environmental conditions, amount and oxidation state. As a rule of thumb, silver is generally cytotoxic as it catalyzes ROS (reactive oxygen species) production in the presence of oxygen species [136], while Ag_2O nanoparticles are often reported to be biocompatible [137]. Copper, on the other hand, is cytotoxic in oxide (II) form [138] and possibly biocompatible in its oxide (I) form [139].

Up until the eighteenth century, ivory teeth were the most commonly used in restoration, even if they had many drawbacks such as their degradation over time and the fact that they could be easily stained. To overcome these limitations, the British doctor Alexis Duchateau began investigating mineral alternatives [141]. With the help of porcelain manufacturers, he was able to make a set of such dentures in 1774, but his original idea was soon learned and further developed by Nicolas Dubois de Chémant, who is given credit for being the first dentist to successfully insert mineral teeth in the human mouth. Early mineral paste or porcelain dentures were made in one piece [140], and most resulted in failure, but on the last decade of e the eighteenth century de Chémant started to use platinum pins and rings to fix his artificial teeth (Fig. 7) [current location: La Cité de la Céramique – Sèvres et Limoges, Sèvres, France] [142]. By 1825 Samuel Stockton, in Philadelphia, was manufacturing half a million porcelain teeth a year, soon followed by his nephew, White [143], who opened his own company in 1844, further improving the quality of the product.

Giuseppangelo Fonzi (1768–1840) was an Italian dentist who moved to Paris to improve his knowledge and ended up working for Spanish, French, Russian and Bavarian monarchies. Fonzi's greatest achievement was probably the development of "terrometallic teeth" [63], artificial ceramic crowns that could be implanted directly into the socket using platinum hooks, making them not only aesthetic and functional, but also unalterable over time. Some of these early artificial ceramic crowns are displayed at the "Historical Dental Museum Collection" of the Kornberg School of Dentistry, Temple University, United States. Fonzi noted that, by applying small alterations to the composition of the ceramic, he could obtain up to 26 shades of color to match the original teeth of the patient.

Following the results of Fonzi, in 1837, English goldsmith Claudius Ash begun to manufacture his own version of dental implants secured over platinum metal posts (Fig. 8). Ash produced several versions of his implant, with one or multiple false teeth, which he sold under the name of "Ash's tube teeth" [144]. In 1885 Logan finally introduced the Richmond Crown,

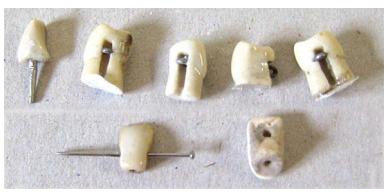

Fig. 7 False teeth realized by Nicolas Dubois de Chémant, reprinted with permission from [140]

Fig. 8 Claudius Ash's tube teeth. Current location: Science Museum, London, England

in which porcelain was fused to the platinum post and, just 1 year later, Land made a further improvement in the design making the first fused porcelain inlay and crown backed by platinum foil. Porcelain restorations gained a little further momentum which lasted until the development of the vacuum fired dense translucent ceramic porcelain teeth, in 1949 [145].

Similar to gold, the biocompatibility of platinum is granted by its intrinsic inertness: it does not rust when in contact with biological fluids and it does not interfere with biological processes [146]. Moreover, there are no reported cases of allergic reactions to platinum.

The oldest European mention of amalgams is probably from Stocker [147] (reported in Latin language as Joannis Stocker or Ioannis Stockeri), who, in 1659, boiling together blue vitriol and mercury.

Jean D'arcet (1724–1801) was a French chemist and politician. He contributed to the advancement of industrial processes for producing and improving metal alloys such as bronze, but also new extraction methods for precious metals. In the beginning of the nineteenth century the so-called d'Arcet's metal, a low melting point (about 100 °C) alloy consisting of bismuth lead and tin was applied for the first time in dentistry. From the metallurgical point of view, the ternary system xPb-yBi-zSn is extremely interesting as it does indeed possesses a minimum melting temperature of 100 °C, but only at around $x = 0.35$, $y = 0.50$ and $z = 0.15$ [148], making its chemical composition somehow more complex to optimize when compared to most mercury-based amalgams. Moreover, the d'Arcet's metal caused both pain and damage when it was poured into a cavity [114]. In 1818, in order to further reduce the melting temperature of the alloy, Louis Regnart, a member of an ancient family of dentists, added small amounts of mercury to the d'Arcet's metal. The new chemical composition, which made him famous as the "father of the amalgam," melted at only 68 °C [114].

Many literature references consider August Onesime Taveau the first dentist to use amalgam as a dental

restorative material, despite starting his research activity more or less 10 years after Regnart. Taveau created the "Pate d'Argent," an amalgam of silver coin filings with low mercury content, which needed to be heated before application. It must be noted that an alloy containing just silver and mercury would require high amounts of mercury to be properly shaped at relatively low temperatures, and the method of Taveau was actually successful only because silver coins already contained a low amount of tin [149]. The main drawback of Taveau's amalgam was its stability: the material expanded in situ, often resulting in early failures.

The English chemist Charles Bell in 1819 also made his own version of the silver amalgam, originally named simply "Bell's putty" and later on "Mineral Succedaneum," meaning "mineral substitute".

In the early 1830s a family of charlatans from London, the Crawcours, realizing the commercial potentiality of "Bell's putty," started their own dental business [150]. Advertising that they filled teeth with the "Royal Mineral Succedaneum in 2 min without any pain, inconvenience or pressure" they enjoyed a brief period of economic success. Obviously, the attribute "Royal" was meant to suggest that the material was an equivalent substitute for gold, which was still the standard material for dental fillings at the time. The five brothers, thanks to their excellent promotional abilities, were able to sell a product with actual very poor clinical results, in particular over time. Most of the fillings were doomed to fall out or to crack the teeth due to the natural expansion of the material. The few that remained in situ, often lead to the decay of teeth as the Crawcours did not practice excavation of caries or any kind of cavity preparation.

To further expand their successful business, two of the Crawcour brothers moved to the United States where they encountered a strong opposition from the established dentists. American professionals had been using gold fillings for decades and felt their business could be threatened by the much cheaper competitors. Making use of amalgam became synonymous with quackery, and a professional association, the American Society of Dental Surgeons, was founded in 1840 to counteract the innovation and protect the consolidated quality standards of the profession. To be accepted as a member the dentist had to sign a statement that he did not use amalgam and by 1847 eleven members of the society were expelled because they refused to sign. When the American Society of Dental Surgeons was formed it did not initially required dentists to sign a non-amalgam use pledge, but the rule was instituted at a later time. As a result, most dentists refused to sign the pledge and did not renew their membership in the society. A few years later the society had to disband due to the lack of being able to establish a quorum at annual meetings. Despite the charlatanical nature of the Crawcours' business, amalgam supporters grew in numbers over the years.

By 1841 Linlott [151] published a "letter of concern" in "The Lancet" (England), pointing out that "Mineral Succedaneum" (in 1841 already sold with many other commercial names) was nothing but a misused alloy of quicksilver (mercury) containing bismuth, tin, silver, often obtained just by filing a half-crown. The more reliable and stable results were obtained with pure silver precipitates, but the half-crown of the time only contained 92.5% of silver. Linlott further noticed that "if exposed to the action of the fluids of the mouth, it quickly assumes a bluish-black tint, and greatly discolors the tooth into which it has been introduced." Despite being commercialized as similar products, the actual compositions and short/long time performances of these materials varied greatly, making only the use of a few commercial products justifiable.

Many patients could not afford the expensive gold fillings or endure the great pain the gold mallet caused. Thus, the opinion of the profession became so seriously divided that, in the United States, it gave rise to what has been called the Amalgam War. The bad reputation of the Crawcour's product greatly contributed to the skepticism about dental amalgams, but the heart of the controversy was more a matter of personal faith rather than that of a concrete scientific concern.

Those against the use of amalgams accused mercury of being the source of various health-related issues, taking also advantage of the bad reputation it acquired for its side effects during the treatment of syphilis. Mercury (in particular as mercury chloride) did indeed kill *Treponema pallidum* bacteria prior to the first use of penicillin, but also caused severe mercury intoxication in about one third of the patients [152].

Other appalling case histories were published not just in gossip magazines but also in reputable scientific journals, sometimes even as editorials. One of the earliest dentists to speak out against the use of amalgam in 1874, and probably the most radical, was Dr. J. Payne, who claimed the dental profession was poisoning "thousands of people all over the world from corrosive sublimate generated in the mouth from amalgam plugs in the teeth." He also claimed that the "quick-silver in the plugs is driven off by the heat in the mouth in very minute particles, and, combining with the chlorine in the fluids of the mouth, or any saline substance, such as our food, passed into the stomach, and produces slow poisoning." and added that "neither Asiatic cholera, nor smallpox, nor any malarious disease is half the mischief… that is done by this poisoning… a person poisoned in this way is

able to be treated for dyspepsia, neuralgia, paralysis, consumption and numerous throat diseases" [153].

Despite the first part of Payne's message being scientifically sound, the second appears as a deliberate exaggeration of the adverse reactions that could be associated with small amounts of mercury released into the human body.

Amalgam at that time, surely, was a very inferior product when compared to modern compositions or even to the best standard of the time (gold). One more reason of concern was the variability in chemical composition: dentists made their very own alloys, usually by filing "silver" coins without even knowing exactly their chemical composition, as that also changed depending on the coin used, going from pure silver to 92.5% silver alloys.

In 1881, Foster Flagg published the result of his systematic studies in the book "Plastics and Plastic Filling: As Pertaining to the Filling of All Cavities of Decay in Teeth Below Medium in Structure, and to Difficult and Inaccessible Cavities in Teeth of All Grades of Structure" [154] where it pointed out the existence of two schools of dentistry, the "gold-work" and the "plastics" and the differences in both processes and objectives. It must be noted that at the time "plastics" was not referred to polymeric materials, but to any easily moldable material, such as the ones used in dental restoration, such as Bakelite or guttapercha. Flagg was a supporter of such "plastics" and amalgams, in particular in order to save teeth even when in "bad shape," and did not understand the advantages of gold-filling going as far as saying that "In proportion as teeth need saving, gold is the worst material to use."

In his record, he notes that Elisha Townsend, president of the American Society of Dental Surgeons in 1855, proposed a new formula for amalgam in order to restore its reputation, as he recognized the value in saving teeth that could not be saved using gold. The new formula contained higher amounts of tin, reducing discoloration but increasing alloy shrinkage. Flagg noted better results when using his own formula, based on 9 parts of tin to 13 of silver (against the 6:4 proposed by Townsend).

After Townsend, many researches proposed new compositions for the fillers, based on silver, tin, copper, gold, platinum and even cadmium, all with more or less the same ratio of tin to silver but with lower shrinkages when compared to the original Townsend amalgam. Some of these alloys improved hardness, others prevented color changes, some other had better edge strength.

The Electro-Chemical Theory, proposed by Dr. S.B. Palmer, further supported the advantages of amalgam and plastics against gold: Palmer attributed the failure in operations mainly to "incompatibility of filling material with tooth—bone" and the reason behind this incompatibility was the idea that every tooth filled with metal was a miniature battery and galvanic currents were powerful agents of decomposition, with dentine acting as the "corroded" side of the battery [155].

Systematic studies like the ones proposed by Foster were uncommon for dentists of the time. The next scientist to present results on new amalgam compositions in a similar fashion would be Greene Vardiman Black, often known as "the father of operative dentistry" [156], many years later. Black is better known for the standardization of dental procedures [157], the classification of dental caries [158] and his studies of dental anatomies [159]. Unlike most clinicians at the time, he advocated for a conservative approach to tooth restorations, emphasizing the removal of only the damaged or decayed portions of a tooth, introducing the concept of "extension for prevention," where the preparation of a cavity extends only to areas that are susceptible to decay, helping preserve healthy tooth structure. Moreover, he researched how much force the masticatory muscles could exert by using a "gnathodynamometer," and then continued with studying the stress of mastication while chewing foods such as bread, steak and various vegetables. For ascertaining the volume changes of the amalgams during the setting, he also constructed a dedicated device.

Black tested many amalgams with different compositions, and finally proposed to keep the content of silver between 65 and 70%, 25–28% of tin, 3–5% of copper and 0.5–2% of zinc [160]. The formula of Black did not expand or contract and had enough strength to withstand the masticatory forces. Despite the exceptional results, dentists soon began to complain about the alloy could only be used fresh and when stored resulted in irregular fillings. To fix this problem, the alloys had to be properly annealed.

The main advantage of dental amalgams has been their processability, but what was supposed to make dental amalgams biocompatible was their intrinsic stability in biological environments. Nevertheless, unlike the "d'Arcet's metal," amalgams can be obtained in a wide range of chemical compositions, not all of which can nowadays be considered "biocompatible," in particular over long time spans. Most amalgams are subject to tarnishing and corrosion in the oral environment over time, a problem that still affects modern, optimized alloys [161]. Mercury-rich phases are more prone to chemical attack, and this might affect the surrounding biological environment [162]. Moreover, amalgam corrosion products can penetrate into dentine and cause discoloration demineralization [163]. Again, as observed before, what controls the biocompatibility of mercury amalgams are the chemo-physical properties of the surfaces: as soon as a stable oxide layer is formed on the surface of the alloy,

the release of mercury in the environment is drastically reduced [164].

Foster Flagg also advised the use of gutta-percha in root canal filling: at the beginning it was suggested as a temporary filling for fragile teeth, mainly because of its ease of manipulation, its high degree of biocompatibility and the conducting quality. Gutta-percha is very stable in most biological environments, especially when in contact with mouth fluids, and also possesses a certain level of wear resistance. Gutta-percha is technically a natural polyterpene, a polymer of isoprene and polyisoprene, specifically trans-1,4-polyisoprene [165]. Despite being chemically similar to natural rubber (cis-1,4-polyisoprene) [166], gutta-percha crystalizes, leading to a more rigid material. Gutta-percha exists in alpha and beta forms, with the alpha being more brittle at room temperature [167].

Since the late nineteenth century, dental-grade gutta-percha has been sold in three commercial grades: the first, known as "low heat" had sufficient plasticity for manipulation at temperatures ranging from 60° to 95 °C.

The second, known as "medium grade," could be manipulated at temperatures of about 95–100 °C and was considered the best grade for general use by Flagg, as it could be easily warmed over water. It possessed sufficient mechanical resistance and durability to be applied in vivo and was considered to produce excellent and durable fillings.

The last, known as "high heat grade," could not be manipulated at temperatures under 102 °C which made it less convenient for general use as it needed to be heated up using an oil lamp or a stove.

One of the main drawbacks of gutta-percha was its color: the original dark brown was considered to be esthetically unpleasant to the general public. To improve its color, gutta-percha was often mixed with other ingredients such as quicklime (oxides of calcium and magnesium) or silex (ground stone, especially from silica or silicates).

Flagg further remarks that gutta-percha was initially introduced as a temporary filling material, but soon many professionals noticed that gutta-percha fillings can actually work as permanent treatments and in some cases they could even outlast their direct competitors, the gold fillings.

Gutta-percha is possibly the oldest plant-based dental material to still be in use today [168]. Modern, commercially available products have often a gutta-percha content of less than 25% in mass, with zinc oxide contents of up to 60% followed by metal sulfates, zinc chloride and waxes/resins [169]. Zinc oxide is used as a filler, but also to improve elasticity and reduce brittleness, barium sulfate provides radiopacity, while the waxes and resins are plasticizers. Despite the chemical similarities, gutta-percha products seem not to induce allergic symptoms in individuals sensitized to natural rubber latex, where the allergy is actually caused by residual proteins [170].

Cis-1,4-polyisoprene soon followed his trans- cousin in the world of dentistry, but with a quite different application. In 1851, Nelson Goodyear, brother to the more famous Charles, developed and patented a manufacturing process for making hard rubber, which he named Vulcanite. As early as 1853, the first Vulcanite denture base for porcelain teeth was produced, and at the time vulcanite prostheses could cost only one third of those made of either metal or ceramic. The advantages of Vulcanite were its ease of formability, good adaptation to the master cast, and insolubility and non-reactivity in saliva. Its major drawback was that of color: in its processed state, Vulcanite was a dark brown to gray material, and the color could not be further optimized without hindering the mechanical properties or the chemical resistance [171].

But polyisoprene was not the only biocompatible polymer known at the time: cellulose nitrate, derived from plant framework, was manufactured commercially in England as early as 1866 [172] and just a few years later, in 1869, John Wesley Hyatt, an American inventor, created celluloid initially as a substitute for ivory in the production of billiard balls. Celluloid was introduced in dentistry in the same year [173], when Vulcanite licensing battles were ongoing [171] and, despite requiring complex processing, its overall costs were lower considering the purchasing of a Vulcanite license and paying the per-tooth fee [174]. Despite having a more natural gingival color when compared to Vulcanite, celluloid was not as stable: it changed shape, it turned greenish and it developed a bad smell over time.

Another commonly used plant-based product of the time was sandarac varnish: extracted from the resin of *Tetraclinis articulata*, native to the northwest of Africa, it could be used both as a sealant or a bonding agent [175], temporarily or permanently.

The biggest biological concern about polymers used in dental or orthopedic applications is indeed their chemical and/or biological stability over time: Vulcanite tended to become unhygienic over time due to the uptake of saliva [176], gutta-percha possesses some degree of toxicity [177], in particular for high contents of zinc oxide, celluloid could be degraded by salivary enzymes. All these problems, which were common with nineteenth century polymers, have yet to be completely solved even in modern formulations [178].

It should be noted that some of the additives found in modern gutta-percha were also commonly applied in dentistry at the time of Flagg: zinc oxy-chloride, also

known as "cement plombe," has been used as a dental filling material since the first half of the nineteenth century, often with conflicting results, in particular due to its solubility in weak acids [179, 180]. Kirk and Kokomo [181] noted that "[…] the fluid permeates the tubuli and preserves the whole tooth-structure as nothing else can," but also advised for care during use as it could cause inflammation.

Lead is highly toxic and this knowledge dates back to the second century BC [182]. Still, lead has been used in oral biomedical devices at least until the nineteenth century. The technological sophistication of eighteenth century dentistry is well represented in the only surviving complete set of president Washington's dentures, commissioned (or, less likely, manufactured, as reported by some sources [183]) between 1790 and 1799 by his personal dentist, John Greenwood [184] [current location: George Washington's Mount Vernon, Mount Vernon, United States]. The dentures consist of two cast-lead bases that fit against the upper and lower jaws. Each of the teeth has a hole drilled through it so that it could be attached to the base using a brass wire. The two bases are connected to each other by using two coil springs that allow the dentures to move up and down inside the mouth. Other dentures commissioned by John Greenwood for Washington made use of gold [current location: Dr. Samuel D. Harris National Museum of Dentistry. Note that after being reportedly stolen in 1981 [185], only the bottom half was recovered in 1982 [186], but lead is both lighter and easier to shape.

The toxicity of lead is a source of concern and we have solid proof that lead dissolves in human saliva [187]. The use of lead was probably justified (at the time) by the temporary nature of the dentures, which were only to be wore in public. Moreover, Washington's dentures were often modified and improved, so the overall exposure was limited. As we stated in the second section, time is a crucial parameter in the assessment of biocompatibility.

Cheoplastic is nowadays the definition of any alloy that fuses at low temperatures and can be used for molding artificial teeth, such as lead. Nevertheless, during the nineteenth century the term was associated with an alloy patented by Alfred Blandy in 1857 [188]. Other alloys, for example aluminum based, were available at the time [189], but despite being easy to form gave unsatisfactory results. Blandy's cheoplastic was an alloy of tin containing also silver, bismuth and antimony and it was initially regarded quite highly by professionals, at least until Wood pointed out the chemical weakness of the alloy against various diluted acids [190]. Concerns were raised also for the content of arsenic, which is always present with antimony. Apart from the formability, another advantage of cheoplastic is the possibility to cast the alloy directly on the tooth instead of grinding the tooth to fit the metal [191].

Tin has a certain resistance to aggressive environments, thanks to the formation of a protective layer of SnO_2, but the protection offered is much weaker compared to stainless steel, titanium, tantalum or cobalt-chrome alloys. At the time, tin could only be compared with silver, with the latter being more prone to tarnishing and the former mechanically weaker. The biocompatibility of SnO_2 makes tin alloys not toxic even when heavily corroded, but the process compromises stability and can also lead to the release of other, more dangerous elements.

Dr. McCelland introduced Rose Pearl as a base material around 1860. Another dentist, C.M. Wright, noted that it "is fine grained semi-translucent, elastic and inodorous, and can be successfully manipulated by any dentist who can make good gold work" [192]. Rose pearl was in reality a solid compound prepared by treating vegetable fiber, such as cotton, with nitric acid and sulphuric acid [183], which is chemically very close to cellulose nitrate, to the point that legal issues were raised about the originality of the invention [193].

Dr. McCelland claimed that Rose Pearl was twice as strong as Vulcanite, could withstand the action of acids, possessed qualities of elasticity, strength and durability, was not easily broken and could be adapted to the mouth nicely. It also possessed a natural pink color, so it was aesthetically more pleasant than the other alternatives on the market at the time. Still, it was subject to shrinkage after setting, so it was used relatively briefly.

Despite being replaced, as a denture base, by more robust materials, cellulose nitrate is still used as a biomaterial, mainly for membranes [194], and in particular for wound healing.

The first half of the twentieth century

A second "war" against dental amalgams started in 1926: the German chemist Alfred Stock, in his article "Die Gefahrlichkeit des Quecksilberdampfes und der Amalgame," pointed out the potential dangers of the mercury vapors generated from amalgams. The paper opened a new discussion on the biocompatibility of dental amalgams, as it alarmed professionals and scientists both in Europe and in the US. The new born skepticism against amalgams did not reach its peak until the 1970s, but many unfounded claims were spread around the world and the dentists, probably with the best intentions, started to discourage the use of amalgams. Luckily, in the second half of the century new, strong and stable filling materials have been constantly developed, but their composition and biocompatibility is outside of the scope of this review.

The twentieth century is the era of dental polymers and advanced alloys, starting from Bakelite. Formally Polyoxybenzylmethylenglycolanhydride, Bakelite is a thermosetting phenol formaldehyde resin formed from a condensation reaction of phenol with formaldehyde. Developed by Leo Baekland in 1907, it was officially patented in 1909 and used in dentistry for the first time in 1924 [195]. Bakelite denture bases were considered aesthetically pleasant immediately after processing, but had a poor taste due to the presence of phenols, stained very early, were prone to fracture and hand a poor shelf life [196].

The "mummifying" action of the paraformaldehyde and its antiseptic and antimicrobial properties made materials based on Bakelite an attractive choice in endodontics. A series of in vitro studies have shown that these substances have cytotoxic and mutagenic effects. Another resin formulation widely used in many parts of the world, until recently is the resorcinol–formaldehyde type. A variant of the phenol–formaldehyde or Bakelite resin, this sealer is strongly antibacterial, but shrinks and leaves a reddish hue on the surrounding tooth structure (hence the nickname 'Russian Red') [197].

Despite being discovered (twice) in the nineteenth century, polyvinyl chloride, a co-polymer of vinyl chloride and vinyl acetate was introduced as a denture base material only in 1930. Polyvinyl chloride dentures, often obtained by mixing the polymer with calcium stearate, zinc oxide and plasticizers, were observed to harden with time in vivo, forming also fissures and potentially releasing additives into the saliva [198]. Still, polyvinyl chloride dentures were aesthetically pleasant, dimensionally stable during processing, did not absorb moisture and could bond well with acrylic resins. Generally speaking, the biocompatibility of polyvinyl chloride is considered good and improved formulations are still in use today.

In 1937 Walter Wright introduced poly (methyl methacrylate) (PMMA) as a denture base material, having found that it fulfilled all the requirements [199]. The materials soon became popular and by the 1940s almost all dentures were fabricated with acrylic resins. Even when new materials were introduced later on, PMMA remained the preferred choice for both complete and partial denture prostheses. The material eventually made it into arthroprosthesics when John Charnley, an eminent figure in this field in the twentieth century, started using it as bone cement to fix hip implants and to repair fractures [200, 201]. PMMA is a clear and colorless polymer with high stability that can be polymerized using three different methods: heat, catalysts or light, making it a flexible choice that can be adapted to the situation.

Despite being considered inert, as most other polymers described to date, PMMA was also subject to unexpected degradation in vivo, resulting in moisture uptake, hydrolysis of ester groups and release of monomer over time [202].

PMMA was not the only acrylic resin to be tested at the time: Plastupalat, a German product which was obtained by copolymerization of 65 parts of methyl methacrylate with 65 parts of butyl ester of acrylic acid, was also used in similar applications, as well as many other variations in composition. Neo-plastupalat, in particular, was reported to be more hydrophobic than other formulations, resulting in less adulteration, discoloration, scaling, contamination and malodor [203].

A review on the use of acrylic resin, dated back to 1949, concluded that despite being tested as denture based materials, their use was soon extended into tooth restorations of all types, artificial teeth, instruments, trays and numerous other purposes [204].

On the 13th of August 1913, Harry Brearley of Sheffield, mixing 12.8% of chromium in a steel containing about 0.24% of carbon discovered what we now call "stainless steel." In just a few decades, this accidental discovery completely reshaped the world. In the field of dentistry, stainless steel has been used both for crowns and for temporary devices such as retainers and braces. Stainless steel devices had many advantages over gold: its color was more desirable and it could be polished quickly. Stainless steel mechanical strength and resistance to abrasion was also much higher when compared to any other material in use at the time, making it an ideal candidate for use in biomedical devices [205]. Moreover, stainless steel was much cheaper than gold, and thus much less likely to be stolen. Overall, the properties of stainless steels are superior to other alloys that, in more modern formulations, it is still in use nowadays.

The biocompatibility of stainless steel is based on the protective function of the chromium-rich oxide layer at its outermost surface: as long as the layer is intact, potentially toxic elements like chromium and nickel will not be able to leak. The layer has self-healing capabilities in humid environments, but still a combination of mechanical and chemical stress might cause a slow release of toxic elements or particulates.

Cobalt chrome alloys were discovered by Elwood Haynes at the beginning of the twentieth century. The alloy was capable of resisting oxidation and corrosive fumes and exhibited no visible sign of tarnish even in extreme conditions, such as boiling nitric acid. Under the commercial name of "Stellite" (containing more than 30% of chromium and the remaining part tungsten), the alloy has been used in various applications requiring wear resistance, such as for cutlery, bearings and blades. The alloy soon showed promising results also in the field of dentistry, where both chemical and mechanical

resistance was required. Despite the high melting point, Stellite dentures were also cheaper than their gold or platinum counterparts on the market [206], while Stellite wires were preferred for retainers compared to other alloys because of their combination of high mechanical strength and elastic modulus [207].

Vitallium, another cobalt alloy, this time containing 30% chromium and 5% of molybdenum developed by Albert W. Merrick in 1932, soon took over Stellite, and became the most common cobalt alloy for dental applications. One of the reasons for the success of Vitallium has been the lower risk for secondary inflammatory reactions, as reported by the practitioners of the time [208], who also referred to Vitallium as "the most inert alloy currently used in surgery" [209]. Apart from retainers and braces and dentures, Vitallium was also utilized for dental screws that, combined with ceramic crowns become more and more popular over the century, as they resulted in being well tolerated by the human body, when their size was chosen carefully [210].

Both Stellite and Vitallium's biocompatibility is based on the thin layer of chromium oxide on their surface, just as for stainless steel. But cobalt-chrome's protective layer is usually more resistant to chemical attack [211], making the former more inert in biological applications. Moreover, cobalt-chrome alloys are also harder and stiffer, reducing the amount of wear produced by constant use.

Conclusions and remarks

This review covers more than 30 centuries of technological advances in the field of oral biomaterials, going from Egyptian gold-wire appliances to advanced cobalt alloys and polymer formulations that are still in use today.

With the noticeable exception of the transplantation of teeth, it was not until the second half of the twentieth century that bioactive materials were actually studied or developed and, on the contrary, the search for biocompatibility moved towards bio-inertness, to the point that biomaterials were initially defined only as bio-inert substances. Bio-inertness represented a "safer" route for implantation as it reduced the risks for rejection, especially at a time when the mechanisms of infections and immunological responses were yet to be discovered.

It is also interesting to notice that probably the first biomaterial to be used in this field, gold, has been constantly and successfully applied for more than two millennia in all kinds of dental and prosthetic devices. The chemical inalterability of gold, along with its resistance to pathogenic colonization, made these devices more successful than any other competing material, over the centuries.

In the second half of the twentieth century, which is not covered in this review, the paradigm started to shift from bio-inertness to bio-activeness, as it was finally understood that materials can play an active role in the success of the procedure. Bio-activeness comes (literally) at a price: it is by far more difficult and expensive to develop a well-balanced bioactive material as it requires a fine understanding of the biological environment, as well as longer trials. Moreover, most bioactive materials do not possess the same mechanical properties of their inert counterparts, making them less reliable as standalone solutions.

Biocompatibility, either in the form of bio-inertness or bio-activity, is controlled by the chemistry and morphology of the outermost surface, making it possible to apply bio-active layers onto otherwise bio-inert materials, thus combining the best of the two worlds into long-lasting and reliable solutions.

Abbreviations

AD	*Anno Domini*
BC	Before current (era) or Before Christ
PMMA	Poly (methyl methacrylate)
ROS	Reactive oxygen species
CT	Computerized tomography

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