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Systemic and Local Tissue Response to Titanium Corrosion

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1. Introduction

The term biomaterials refers to materials that have been designed to be implanted or placed inside a live system with the aims to substitute or regenerate tissue and tissue functions. Williams defines biomaterials as those that are used in devices for biomedical use designed to interact with biological systems (Williams, 1986). Classically, biomaterials are divided into four types: polymers, metals, ceramics and natural materials. Two different types of biomaterials can be combined to obtain a fifth type known as composite biomaterials (Abramson et al., 2004). Biomaterials are widely used in orthopedic, dental, cardiovascular, ophthalmological, and reconstructive surgery, among other applications. The discovery of relatively inert metals and alloys has led to their use in the field of biomedical applications such as orthopedics and dentistry, and their use in increasing due to their physical-chemical properties and compatibility with biological surroundings (Ratner et al., 2004). One of the most frequently employed metallic biomaterials is titanium (Anderson et al., 2004). Though zirconium is not widely used as a clinical material, it is chemically closely related to and has several properties in common with titanium (Thomsen et al., 1997). Although both titanium and zirconium are transition metals, their physicochemical properties such as oxidation velocity, interaction with water, crystalline structure, transport properties, and those of their oxides differ quantitatively (Henrich & Cox, 1994); these differences may have an effect on biological response (Thomsen et al., 1997). Indeed, the use of zirconium and zirconium alloys to manufacture implants for traumatological, orthopedic, and dental applications has been reported (Sherepo et al., 2004; Sollazzo et al., 2007).

Titanium and zirconium are highly reactive metals and when exposed to fluid media or air, they quickly develop a layer of titanium dioxide (TiO_2) or zirconium dioxide (ZrO_2). This layer of dioxide forms a boundary at the interface between the biological medium and the metal structure. It produces passivation of the metal, determining the degree of biocompatibility and the biological response to the implant (Kasemo 1983, Kasemo & Lausmaa 1988, Long & Rack, 1998). Titanium dioxide exists naturally, mainly in the form of three crystalline structures: rutile, anatasa, and brookite. In the case of titanium implants, the passive oxide layer is composed of anatase and rutile or anatase alone (Effah et al., 1995; Olmedo et al., 2008a; Sul et al., 2001). Zirconium, however, does not exist as a free metal in nature; it occurs as the minerals zircon, or zirconium silicate ($ZrSiO_4$), and the rare mineral baddeleyite or zirconium dioxide (ZrO_2) which has a monoclinic crystal structure (Zirconium. Mineral Information Institute, 2009). Baddeleyite, also known as zirconia, is the most naturally occurring form and can be transformed into a tetragonal (1100 ºC) or cubic (2370 ºC) crystallographic form depending on temperature (Chowdhury et al., 2007; Manicone et al., 2007).

Titanium is widely used in the manufacture of dental and orthopedic implants due to its excellent biocompatibility. The latter is defined as the ability of a material to perform with an appropriate host response in a specific application (Williams, 1987). The use of titanium dental implants has revolutionized oral implantology. Currently, almost 300,000 patients in the United States have dental implants. In the area of orthopedics, replacement hip joints are implanted in more than 200,000 humans each year (Ratner et al., 2004). Dental implants are surgically inserted into the jaw bone primarily as a prosthetic foundation. The process of integration of titanium with bone was termed "osseointegration" by Brånemark (Brånemark et al., 1977; Chaturvedi, 2009).

No metal or metal alloy is completely inert *in vivo*. Corrosion is the deterioration of a metal due to interaction (electrochemical attack) with its environment, which results in the release of ions into the surrounding microenvironment (Jacobs, 1998). There are "noble" metals such as rhodium (Rd), palladium (Pd), iridium (Ir) and platinum (Pt), whose resistance to corrosion is due to their high thermodynamic stability. Passivating metals, such as titanium (Ti), vanadium (V), zirconium (Zr), niobium (Nb), and tantalum (Ta), however, are thermodynamically unstable and their resistance to corrosion results from the formation of a protective oxide layer on their surface (Lucas et al, 1992). Titanium is available as commercially pure (c.p.) titanium or as Ti-6Al-4V alloy with 6% aluminum and 4% vanadium. The addition of Al and V increases strength and fatigue resistance; however, this may affect the corrosion resistance properties and may result in the release of metal ions (Textor et al., 2001). C.p. titanium and Ti-6Al-4V alloy are the two most common titanium-based implant biomaterials (Abramson et al., 2004). There are four standard types or grades of c.p. titanium used for the manufacture of surgical implants, which differ in their content of interstitial elements. This content determines the mechanical properties of a material: the higher the content the higher the grade. In other words, grade 1 is the most pure and grade 4 contains the greatest amount of impurities and has the greatest mechanical resistance. C.p. titanium is used to manufacture dental implants, whereas a Ti6Al4V alloy is used mostly in orthopedics.

As previously stated, all the metallic materials employed in surgery as permanent implants are liable, to a certain degree, to corrosion due to variations in the internal electrolyte milieu (Jacobs, 1998). Corrosion, one of the possible causes of implant failure, implies the dissolution of the protective oxide layer. When metal particles/ions are released from the implant surface, they can migrate systemically, remain in the intercellular spaces near the site where they were released, or be taken up by macrophages (Olmedo 2003, 2008b). The presence of metallic particles in peri-implant tissues may not only be due to a process of electrochemical corrosion but also to frictional wear, or a synergistic combination of the two.

Moreover, mechanical disruption during insertion, abutment connection, or removal of failing implants has been suggested as a possible cause of the release of particles from metal structures (Flatebø, 2006; Jacobs, 1998). The release of particles/ions from the implant into the surrounding biological compartment, their biodistribution in the body, and their final destination are issues that lie at the center of studies on biocompatibility and biokinetics. The chemical forms of these released elements have not been identified to date. It is unclear whether these products remain as metal ions or metal oxides, or whether they form protein or cell-bound complexes (Brown et al., 1987; Urban et al., 2000). In the particular case of titanium, little is known about the valence with which it exerts its action, the organic or inorganic nature of its ligands, and its potential toxicity (Jacobs, 1991).

The potential toxicity and biological risks associated with ions and/or particles released due to corrosion of metallic implants is a public health concern for the community of patients who have a prosthesis (orthopedic and/or dental), since these prostheses remain inside the body over long periods of time. Likewise, the subject of corrosion is of interest to researchers; corrosion studies aim at avoiding the possible corrosion-related health problems that may arise when metallic implants are placed in humans. Controlling corrosion is most relevant for, in order to protect patient health, corrosion should be negligible. Thus, managing and controlling corrosion of a biomedical implant is a paramount issue from a biological, sanitary, metallurgic, economic and social point of view. The current massive use of these metal biomaterials in the biomedical field renders it necessary to have detailed knowledge not only on their early effects (short term failure) but especially on their long term effects, given that these materials remain inside the patients over long periods of time, sometimes throughout their entire life. With the aims to improve biocompatibility and mechanical resistance, manufacturers of biomedical implants seek to develop an adequate design with minimal degradation, corrosion, dissolution, deformation, and fracture.

The study of corrosion requires an interdisciplinary approach including chemists, biologists, physicists, engineers, metallurgists, and specialists in biomedicine. The Biomaterials Laboratory of the Department of Oral Pathology of the University of Buenos Aires, the National Commission of Atomic Energy and the University of San Martin have been conducting collaborative research on corrosion aimed at evaluating both local tissue response in the peri-implant microenvironment and the systemic effects and possible consequences of corrosion, focusing mainly on dental implants (Olmedo et al., 2009).

2. Local effects of corrosion

As mentioned above, the titanium dioxide layer prevents corrosion. However, this layer is prone to break, releasing ions/ particles into the milieu. The potential risk of corrosion and the detrimental consequences of corrosion byproducts in the surrounding tissue are issues of clinical importance (Kumazawa, 2002).

The Biomaterials Department has a Failed Human Dental Implants Service devoted to the *in situ* evaluation of the interface, which consists of the implant and the peri-implant tissues, using systematic histological studies. Studying the implant-tissue interface allows detecting osseointegration, implant- marrow tissue interface (myelointegration), fibrous tissue (fibrointegration) and/or inflammatory reactions. According to the experience of our laboratory, the most frequent causes of dental implant failure in humans are mobility, fracture of the metal (fatigue), and early exposure (Guglielmotti & Cabrini, 1997). Interestingly, implants that had failed due to metal fatigue were found to show satisfactory osseointegration, in other words, good integration of titanium with bone. This means the implants were successful from a biological point of view (osseointegration) but a clinical failure from a mechanical viewpoint. Studying the peri-implant tissue at the metal/tissue level allows obtaining relevant data to determine the possible cause/causes of implant failure.

2.1 Tissue response at the metal-tissue interface

Throughout their histologic studies of failed dental implants, Guglielmotti & Cabrini (1997) consistently observed metal particles inside osseointegrated bone tissue and bone marrow of implants that had failed due to metal fatigue, thus finding evidence of corrosion of the metal structure. Similarly, Olmedo et al. (2003a) found macrophages loaded with metal-like particles in peri-implant soft tissues of failed human dental implants indicating the occurrence of corrosion processes (Fig. 1 A-B). Microchemical analysis of the metallic particles inside macrophages using X-ray dispersion (EDX) confirmed the presence of titanium. It is noteworthy that a greater number of macrophages loaded with particles was observed in the vicinity of the metal surface than at more distant sites. Likewise, numerous case reports in the literature describe histological evidence of inflammatory response and the presence of metallic ions/particles in the tissues adjacent to orthopedic prostheses of titanium or titanium based alloys (Jacobs, 1998).

Titanium is widely used in oral and maxillofacial materials such as grids, fixation plates, screws, and distractors. According to a number of studies reported in the literature, the removal of titanium miniplates after bone healing is complete is unnecessary precisely due to the excellent biocompatibility and corrosion resistance properties of titanium. This is beneficial to the patient since a second surgery is avoided (Rosenberg et al., 1993). Moreover, some authors suggest that miniplates must be removed only when they cause patient complaints and in cases of wound dehiscence or infection (Rosenberg et al., 1993). However, as mentioned above, no metal or alloy is completely inert *in vivo*. In this regard, some authors claim that titanium miniplates should be removed to allow for physiologic bony adaptation and avoidance of a foreign body reaction (Ferguson, 1960; Katou et al., 1996; Moran et al., 1991; Rosenberg et al., 1993; Young-Kyun et al., 1997).

Thus, whether titanium miniplates or grids should be removed after bone healing is complete remains controversial to date. Bessho & Iizuka (1993) examined 113 titanium miniplates that had been retrieved after miniplate fixation of mandibular fractures, and identified surface depressions apparently caused by pitting corrosion (Matthew et al., 1996). Zaffe et al. (2003) evaluated the pre and post-implantation surface features and surface alterations of titanium grids and plates in patients and observed, among other alterations, the presence of pitting on the surface of one of the grids. Experimental studies analyzing the biological effect of a type of localized corrosion, pitting corrosion, on the peri-implant environment have been conducted at our laboratory (Olmedo, 2008c). Pitting corrosion

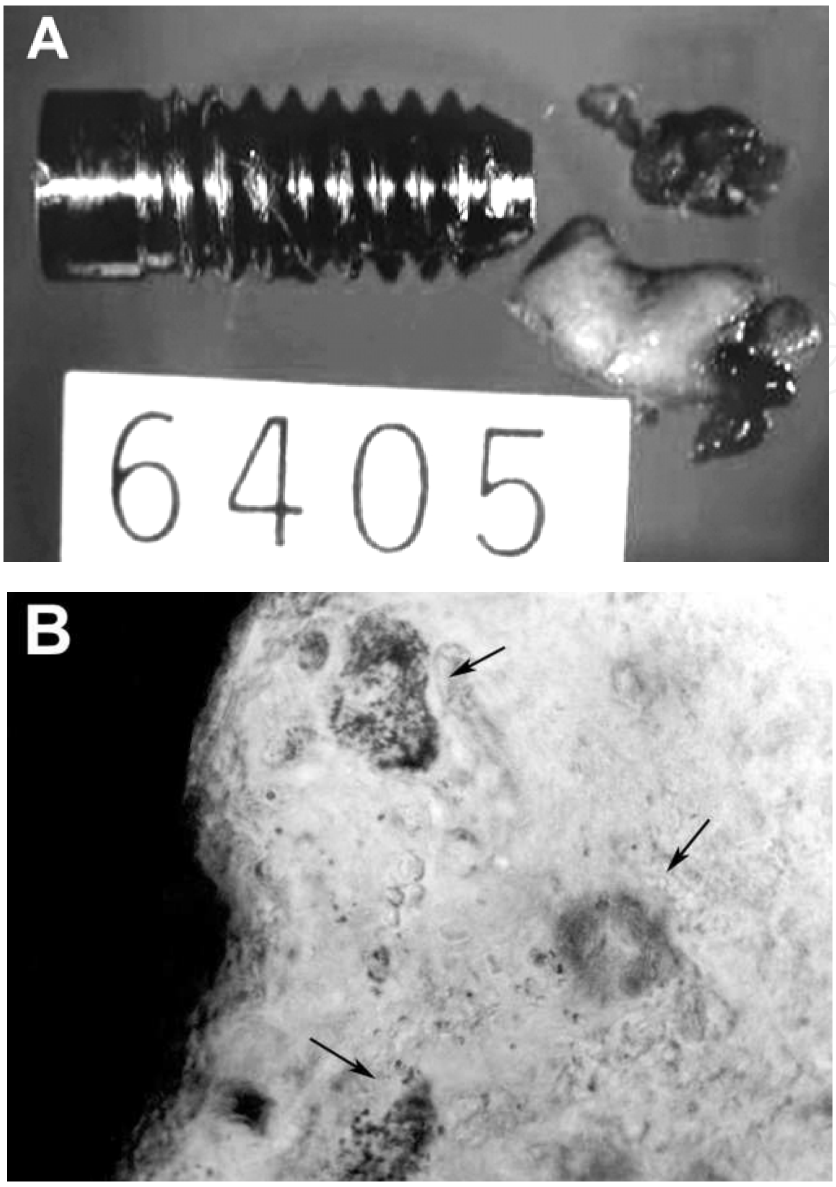

Fig. 1. A) Failed dental implant that shows tissue fragments obtained by curettage of the surgical bed. B) Photomicrograph of macrophages near the surface of the implant (→). Note the presence of particles in their cytoplasm. Ground section. Orig. Mag. X1000

produces local attack, especially on isolated spots of the passivated metal surface, propagating into the metal. The histologic results of our studies showed scarce osseointegration at the bone-implant interface, i.e. the lack of a union between the bone tissue and the surface of the implant; osseointegration was only observed at sites where the metal remained passivated (areas with no pitting and/or surface alterations) (Fig. 2 A,B). The decrease in the percentage of osseointegration in the areas corresponding to the pits would be associated to a change in the chemical composition and/or structure (e.g. crystallography) of the oxide on the pit surface. It is important to point out that the presence of particulate corrosion and wear products in the tissue surrounding the implant may ultimately result in a cascade of events leading to periprosthetic bone loss (Jacobs, 1998; Urban, 1994). The microchemical analysis of corrosion products by energy dispersive x-ray analysis (EDX) in the peri-implant milieu revealed the presence of titanium. It is noteworthy that craters, pits, surface cracks, and depressions may appear during the preparation of the sheets that will be used to manufacture miniplates (Matthew et al., 1996) and may be potential sites for the initiation of corrosion. The results obtained in our study by scanning electron microscopy showed initiation of pitting in areas with surface cracks. Titanium exhibits the greatest resistance to generalized corrosion, pitting corrosion, and crevice corrosion compared to other metals or alloys used in oral surgery, such as stainless steel or chromium-cobalt (Matthew et al., 1996). The severity of corrosion and the quantity of corrosion products that are released may depend not only on the susceptibility to corrosion of the implant material but also on the tissue response to the implant and to the surgical procedures used during implantation (Moberg et al., 1989). The histological results of our study showed the presence of corrosion products around the implant, both outside and phagocytosed in macrophages. In various cases the products of corrosion were found around the blood vessels (Fig. 2 C), in keeping with the histological study of soft tissue adjacent to titanium implants reported by Meachim & Williams (1973) and Torgersen et al. (1995). The observation of metal particles located intracellularly or in association with vessels may represent a biologic response aimed at eliminating the foreign material (Meachim & Williams, 1973; Schliephake et al., 1993; Torgersen et al., 1995).

The properties and quality of the implant material, the shape of the implant, and the handling and surgical procedure are of crucial importance for an optimal biologic performance of any implant device. Unstable conditions in the fracture area after osteosynthesis lead to continuous fretting at the screw/plate interface. Removal of the passivating surface oxide and oxygen depletion in the crevices between plate and screws increase the risk of both crevice corrosion and fretting attack (Williams, 1982). It is speculated that an increased mechanical stability during healing may reduce the fretting component, and thereby reduce corrosion. The adverse local effects caused by pitting corrosion suggest that titanium plates and grids should be used with caution as permanent fixation structures.

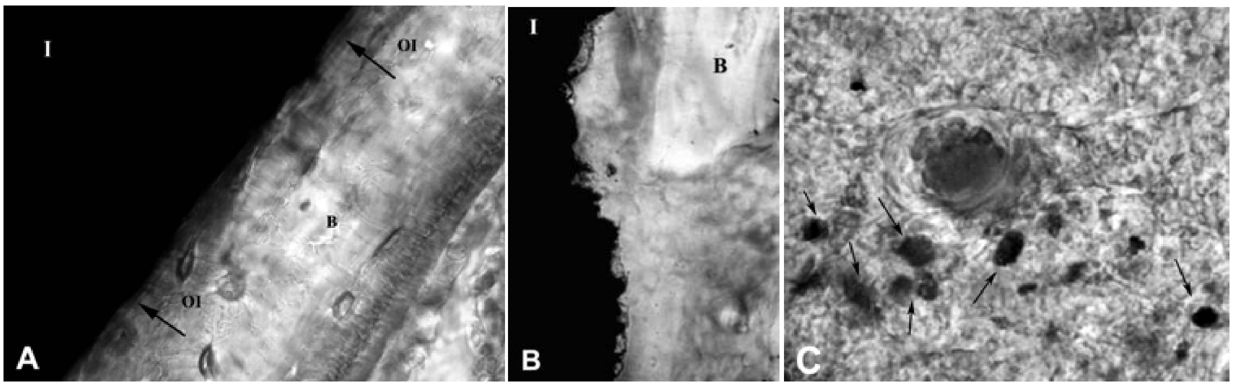

Fig. 2. A and B) Bone tissue-implant interface. A) Control case showing adequate osseointegration (OI) of the bone tissue (B) with the surface of the titanium implant (I). B) Experimental case (pitting corrosion). Note the irregularities on the implant surface (I) and bone tissue (B) far from the surface (lack of osseointegration). C) Blood vessel in the bone marrow near an implant surface and products of corrosion (→) in the vicinity. Ground sections. Orig. Mag. X1000

Based on the aforementioned observations, the occurrence of corrosion phenomena at the interface is of paramount importance to the clinical course of both dental and orthopedic implants since such phenomena could be a possible cause of mid-term implant failure.

2.2 Peri-implant mucosa response

The gingiva around dental implants is called peri-implant mucosa, and consists of well-keratinized oral epithelium, sulcular epithelium, and junctional epithelium with underlying connective tissue. Between the implant surface and epithelial cells are hemidesmosomes and the basal lamina (Newman & Flemming, 1988).

Gingival hyperplasia, mucositis, and peri-implantitis have been described amongst the soft tissue complications associated to dental implants (Adell et al., 1981; Lang et al., 2000). The causes that lead to the development of reactive lesions associated to dental implants have not been fully elucidated to date. In this regard, our research group has reported two clinical cases of reactive lesions in the peri-implant mucosa (inflammatory angiohyperplastic granuloma and peripheral giant cell granuloma) associated to dental implants, in which the presence of metallic particles was detected histologically (Fig. 3 A-B). The presence of metallic particles in the studied tissue suggests that the etiology of the lesions might be attributed to a corrosion process of the metal structure (Olmedo et al., 2010).

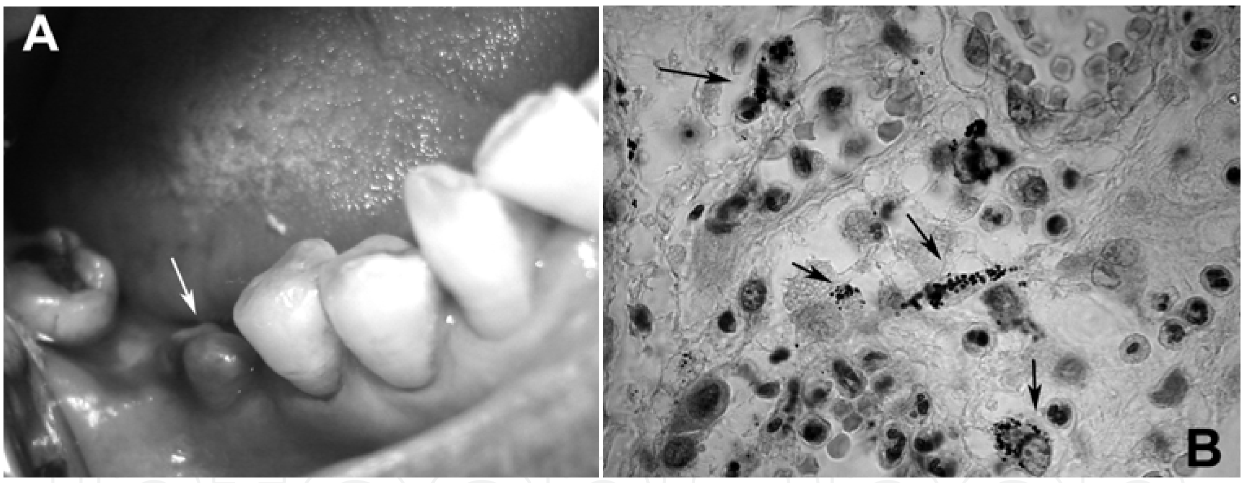

Fig. 3. A) Clinical intraoral photograph showing an exophytic lesion (→) in the area of the first lower right molar. B) Reactive lesion (pyogenic granuloma). Note the significant vascular proliferation and the presence of metal-like particles inside macrophages (→). H-E; Orig. Mag. X400

Abraham et al. (2006) demonstrated the presence of titanium in saliva and gingival fluid of patients carrying titanium dental implants. According to the authors, the highest titanium levels corresponded to patients carrying implants over longer periods of time, thus indicating that titanium accumulates in peri-implant gingival tissue. Oral exfoliative cytology is a diagnostic method which involves the study and interpretation of the features of cells exfoliated from the oral mucosa (Diniz-Freitas et al., 2004). Thus, we performed an exploratory work using exfoliative cytology around the peri-implant mucosa of human dental implants (Nalli et al., 2009). The cytological smears of patients carrying dental implants exhibited metal-like particles varying in quantity, shape, and size. The particles were found both inside and among epithelial cells and macrophages.

The results of the study showed that ions/particles are released from the surface of the implant into the biological milieu. Both epithelial cells and macrophages located in the peri-implant area are able to capture these metal-like particles. Thus, exfoliative cytology is a simple, minimally-invasive, well-tolerated technique, which may prove useful to detect metal particles in cells exfoliated from the peri-implant mucosa, and be a valuable method to monitor dental implant corrosion.

The peri-implant milieu consists of bone tissue, soft tissues, and saliva. Biochemical changes in the peri-implant environment may lead to implant corrosion. According to Abraham et al. (2006) the molecular mechanism of interaction between metal ions and biological molecules or cells remains unclear to date.

The release of ions/particles can cause pigmentation of soft tissues adjacent to an implant (metallosis). Metallosis is defined as aseptic fibrosis, local necrosis, or loosening of a device secondary to metal corrosion and release of wear debris (Black et al., 1990; Bullough, 1994). It involves deposition and build-up of metallic debris in the soft tissues of the body. In a previous study we evaluated histologically tissue response in human oral mucosa associated to submerged titanium implants, using biopsies of the supra-implant oral mucosa adjacent to the implant cover screw (Olmedo et al., 2007a). We observed the presence of different sized particles inside cells or phagocytosed in macrophages in epithelial and connective tissue (Fig. 4 A-B). Interestingly, the titanium particles in the superficial layers of the epithelium might have been associated not only with the cover screw surface but also with other exogenous sources. For example, titanium oxide (TiO_2) is widely used in food products, toothpastes, prophylaxis pastes and abrading and polishing agents, which have been reported in oral biopsies (Koppang et al., 2007).

Microchemical analysis by EDX revealed the presence of titanium in the particles. Immunohistochemical staining with antibodies anti CD68 and anti CD45RO was positive, confirming the presence of macrophages and T lymphocytes associated with the metal particles. In agreement with other reports, (Evrard et al., 2010; Lalor et al., 1991; Matthew et al., 1996;) the T-lymphocyte infiltrate would seem to suggest the presence of an immune response mediated by cells.

Scanning electron microscopy allowed visualizing depressions and irregularities on the surface of the studied metal cover screws. Both unused cover screws and those removed from patients exhibited alterations on their surface. As mentioned previously, craters, pits, surface cracks and depressions may appear during the preparation of the sheets that will be used to manufacture miniplates (Matthew et al., 1996), and be potential sites for the initiation of corrosion. Based on this observation, it would seem advisable for professionals to handle cover screws with utmost care since the observed scratches were most likely caused during placement or removal of the cover screws and could also be potential sites for the initiation of corrosion.

The potential long-term biological effects of particles on soft tissues adjacent to metallic devices should be further investigated as these effects might affect the clinical outcome of the implant.

Corrosion is not only a local problem since the particles released during this process can migrate to distant sites. This issue is of particular interest to biocompatibility studies.

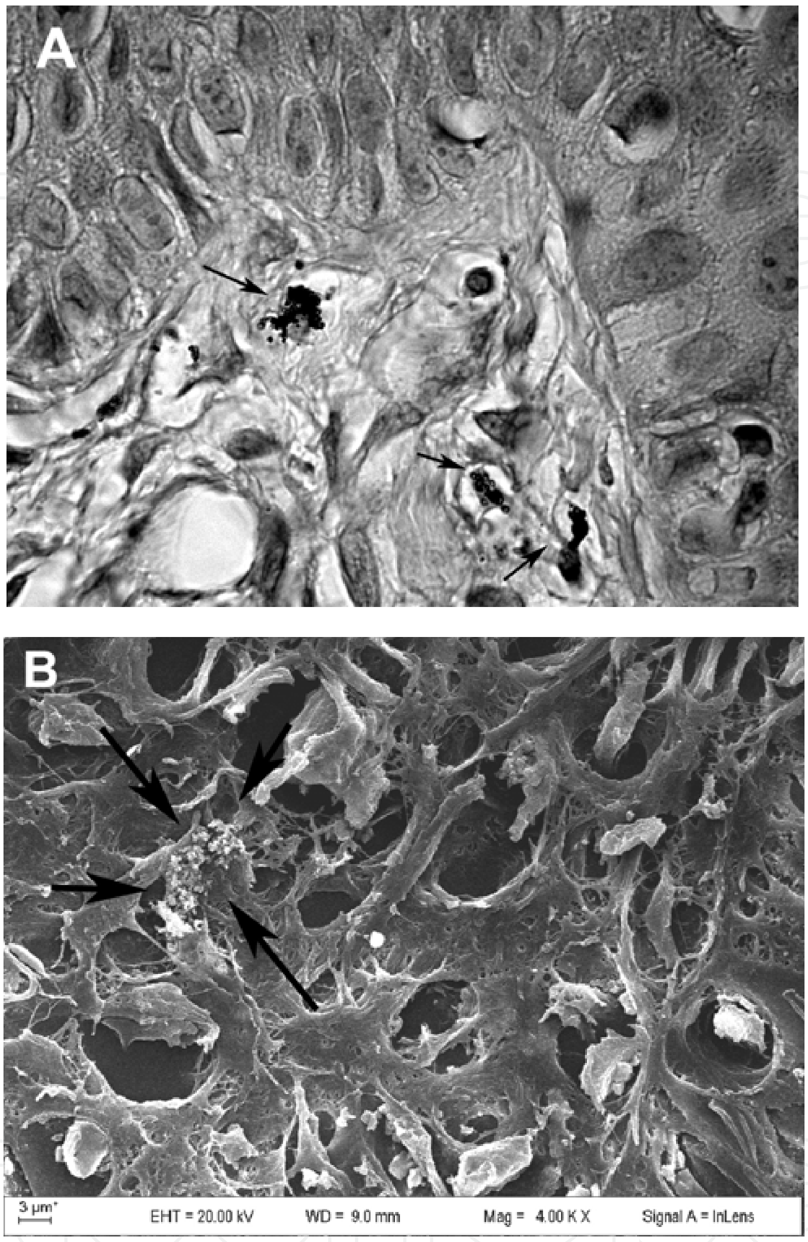

Fig. 4. A) Human oral mucosa covering an implant cover screw. Note the presence of titanium particles (→) inside cells or phagocytosed in macrophages at the epithelium-chorion interface. H-E. Orig. Mag. X1000. B) Scanning Electron Microscopy of an area of mucosa with particles. Note the fine particles (→) among connective tissue elements. Orig. Mag. X4000

3. Studies on the dissemination of titanium towards other biological compartments

The local effect of corrosion and subsequent release of ions/metal-like particles into the peri-implant biological milieu could compromise other biological compartments. The chemically active metal ions/particles may bind to the surrounding tissues but may also bind to proteins and be disseminated in the vascular and lymphatic systems to distant organs (Jacobs et al., 1991; Woodman et al., 1984a).

Studies in the field of orthopedic implants show that titanium ions enter neighboring tissues reaching the internal milieu and are excreted through urine (Jacobs et al., 1991). A number of researchers have found metal ions in body organs and fluids. Jacobs et al. (1991) studied osseointegrated coxofemoral prostheses made of 90% titanium-6%aluminum-4%vanadium and showed that ions of all three metals entered the plasma and were excreted through urine. A study at autopsy by Urban et al (2000) demonstrated the presence of metal-like and plastic particles from coxofemoral and knee-replacement prostheses in the liver, spleen, and lymph nodes.

3.1 Deposition of titanium and zirconium in organs with macrophagic activity. An experimental model

As mentioned previously, titanium and zirconium implants have a protective dioxide (TiO_2 or ZrO_2) layer on their surface. This layer determines biocompatibility and forms a boundary at the interface between the biological milieu and the implant, decreasing their reactivity and partially avoiding corrosion (Jacobs et al., 1998; Kasemo, 1983; Long & Rack, 1998). In order to evaluate the dissemination routes of corrosion products and estimate the intensity of the deposits in different biological compartments, our research group has developed experimental models with animals intraperitoneally injected with TiO_2 or ZrO_2 (Cabrini et al. 2002, 2003; Olmedo et al. 2002, 2003b, 2005, 2008a).

Though it holds true that the experimental doses employed in those studies are high in terms of a normal *in vivo* situation, they served the purpose of our studies since they allow rapid observation of the adverse effects of particles in the studied tissue (Olmedo et al., 2011). Our studies included histologic observation and quantitation of titanium and zirconium deposits in organs with macrophagic activity such as the liver, spleen, and lungs (Fig. 5 A-C), (Olmedo et al., 2002), and showed that at equal doses and experimental times titanium content in organs was consistently higher than zirconium content. Macrophages are cells that respond rapidly to *in vivo* implantation of a biomaterial, including metals, ceramics, cement, and polymers. Their response depends mainly on the size and structure of

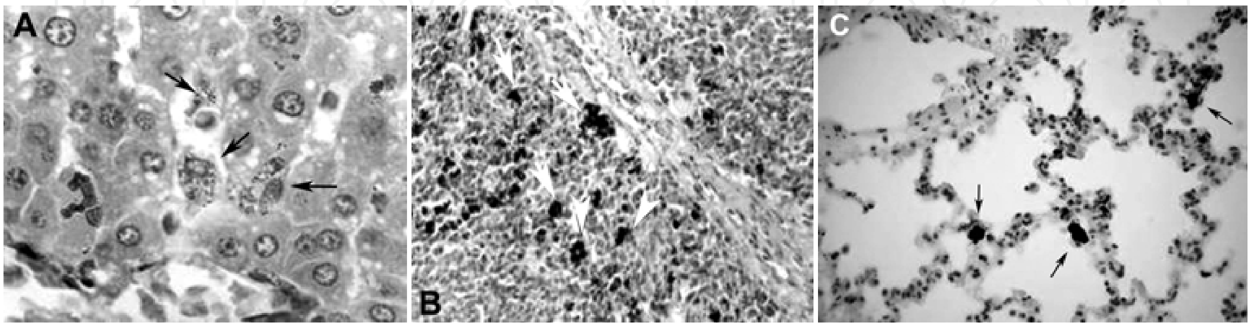

Fig. 5. Titanium deposits in organ parenchyma of an animal injected with TiO_2. A) Liver. Deposition in liver cells (hepatocytes) (→) can be seen clearly. Grenacher carmin stain. Orig. Mag. X400. B and C) Spleen and lung, respectively. Note the amount of titanium (→) deposits. Grenacher carmin stain. Orig. Mag. X400

the material (Anderson et al., 2004; Lu et al., 2002; Solheim et al., 2002; Takebe et al. 2003; Xia & Triffitt, 2006). Particles that are smaller than the macrophages themselves (< 10 m) can be easily phagocytosed. However, the larger particles (10-100 m) are ingested by giant, multinucleate cells (Brodbeck et al., 2005). The biokinetics of TiO_2 and ZrO_2 microparticles depends on differences in physicochemical properties of the particles, such as size, shape and/or crystal structure (Olmedo et al., 2011).

3.2 An experimental model

Experimental studies performed at our laboratory showed the presence of titanium and zirconium particles in monocytes in the blood (Fig. 6) and blood plasma (Olmedo et al., 2003b, 2005). Several transport mechanisms have been described for titanium, e.g. systemic dissemination by the vascular system in solution or as particles (Meachim & Williams, 1973); lymphatic dissemination as free particles or as phagocytosed particles within macrophages (Urban et al., 2000), dissemination of particles to the bone marrow by circulating monocytes, or as minute particles by the vascular system (Engh et al., 1997). Several studies on the bond between metal and proteins have contributed to the understanding of the dissemination of metals. Nickel, chromium, and cobalt would seemingly migrate bound to blood cells and/or proteins in serum and tissue fluids (Brown et al., 1987; Merritt et al., 1984). Aluminum is seemingly transported by transferrin (Alfrey, 1989). Uranium is transported linked to proteins, to citrates and to carbonates (Leggett, 1989).

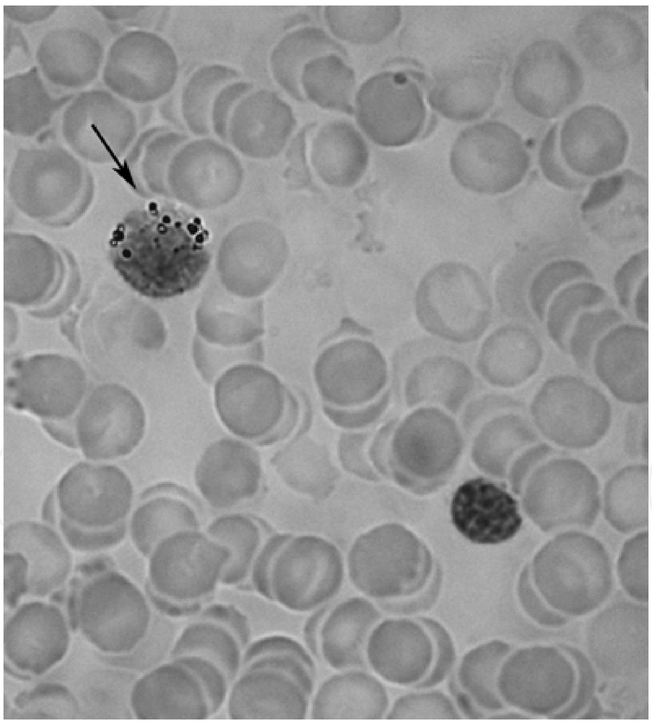

Fig. 6. Blood smear. Titanium particles are evident in a peripheral blood monocyte (→). Safranin stain. Orig. Mag. X1000

The fact that metals bind mainly to albumin would explain their widespread presence in the body. The metallic ions that result from the process of corrosion would thus disseminate to tissues, bind to albumin and enter the circulation exerting their effect at remote sites. Testing for titanium or zirconium in the blood (cells and/or plasma) of patients carrying an implant (coxofemoral implant, dental implant, plates and screws for fracture fixation, metallic panels for reconstructive surgery of large areas of the body) may serve as a method to detect the presence of a corrosion process of the metallic structures (Olmedo et al, 2003b).

3.3 Effect of titanium and zirconium deposition on the lungs: Generation of Superoxide anion (O_2^-) in alveolar macrophages. An experimental model

It is known that trace metals can increase physiological production of reactive oxygen species (ROS) which, without a compensatory increase in antioxidative species, can lead to tissue damage (Gottschling et al., 2002; Kawanishi et al., 2002; Maziere et al., 2003). Studies conducted at our laboratory have shown the presence of titanium and zirconium particles in alveolar phagocytes immunohistochemically identified as CD68 macrophages (Olmedo et al., 2008b). Evaluation of oxidative metabolism of alveolar macrophages exposed to these oxides has shown an increase in generation of ROS. However, it must be pointed out that ROS levels in animals exposed to ZrO_2 were found to be markedly lower than those of animals exposed to TiO_2.

As mentioned previously, the layer of titanium dioxide is crystallographically composed of anatase or a combination of anatase and rutile. Studies on generation of superoxide anion (O_2^-) in alveolar macrophages performed at our laboratory showed that rutile is less bioreactive than anatase. Our results suggest that a rutile coating on metallic biomaterials would improve their biocompatibility properties (Olmedo et al., 2008a).

4. Clinical implications of corrosion

The results of our studies on failed human dental implants and data obtained using the experimental models developed at our laboratory show that any titanium surface can suffer corrosion processes and release particles into the local and systemic biological milieu.

The peri-implant milieu consists of bone tissue, soft tissues, and saliva. Biochemical changes in the peri-implant environment may lead to implant corrosion (Laing, 1973). Thus, titanium implant corrosion is affected not only by the concentration of electrolytes but also by saliva pH (Duffó et al., 1999; Nikolopoulou, 2006) which can vary in areas around dental implants (Meffert et al., 1992). Lotthar et al. (1992) reported that titanium does not withstand a large number of chemical substances. These substances may be in foods, saliva, tooth pastes, and prophylactic agents. They decompose foodstuffs, change plaque metabolism, and cause corrosion (Lotthar et al., 1992; Siirilä & Könönen, 1991). The drop in pH in the electrolytic milieu as a result of local inflammatory processes would seem to stimulate the process of corrosion (Duffó et al., 1999). Abraham et al. (2006) demonstrated the presence of titanium in a wide range of concentrations in saliva and gingival fluid of patients with titanium dental implants.

Significant decreases in pH have been observed in traumatized tissues; indeed pH drops to as low as 4 during the wound healing process (Duffó et al., 1999; Laing, 1973). These low values increase tissue aggressiveness toward the metallic materials. In previous works we found that the decrease in the pH of the electrolytic milieu resulting from local inflammatory processes also stimulates the corrosion process (Duffó et al., 1999).

A corrosion process can decrease the fatigue resistance of the metal compromising metal resistance, which could eventually cause implant fracture (Adya et al., 2005; Guindy et al., 2004 ; Nikolopoulou, 2006 ; Tagger Green et al., 2002). It has been reported that the infiltration of saliva between the suprastructure (nickel-chromium-molybdenum alloy) and the implant (pure titanium) can trigger corrosion processes (galvanic corrosion) due to differences in electrochemical potentials. This causes the release of ions, such as nickel or chromium ions, from the alloy in the crown or bridge to the peri-implant tissues and subsequently results in bone resorption. The latter compromises implant stability, eventually causing implant fracture (Tagger Green et al., 2002).

Metal corrosion can affect the close contact between the implant and the bone tissue (osseointegration). The ions/metallic particles from coxofemoral prostheses can be phagocytosed by macrophages stimulating the release of cytokines, which contribute to bone resorption by activating osteoclasts. In addition to increasing bone resorption, the released particles may inhibit osteoblast function decreasing bone formation and contributing to osteolysis (Allen et al., 1997; Dowd et al., 1995).

The products of metallic implant corrosion behave as haptens generating a hypersensitive reaction that involves the release of inflammatory mediators, known as cytokines, and macrophage recruitment (Hallab et al., 2001; Jiranek et al., 1993; Yang & Merrit, 1994). It remains unclear to date whether it is the hypersensitivity to metal that causes implant failure or vice versa (Hallab et al., 2001). It also remains controversial whether an inflammatory process generates corrosion or whether corrosion triggers an inflammatory reaction. Thus, hypersensitivity to titanium as an implant material in oral and maxillofacial surgery probably occurs more commonly than has been reported in the literature (Matthew & Frame, 1998). There are reports of cases where titanium allergy mainly appeared as the fundamental cause of urticaria, eczema, oedema, redness and pruritus of the skin or mucosa, either localized, at distant sites, or generalized (Sicilia et al, 2008). However, the clinical relevance of allergic reactions in patients with titanium dental implants remains debatable (Javed et al., 2011).

Mineral elements play a critical role in the physiology and pathology of biological systems. Titanium is a nonessential element in that (a) no enzymatic pathway has been elucidated that requires titanium as a cofactor, (b) there does not appear to be any homeostatic control of titanium, and (c) titanium is not invariably detected in the newborn (Woodman et al, 1984b). Thus, the presence of titanium in the body, titanium biokinetics, and the potential biological effects of titanium are of great interest to researchers.

The toxicology of titanium is a current issue of debate. According to epidemiological studies, inhalation of powder containing titanium has no deleterious effect on the lungs (Daum et al., 1977; Ferin & Oberdörster, 1985). Other studies, however, suggest an association between titanium particles and pleural pathologies (Garabrant et al., 1987), granulomatous diseases, and malignant neoplasms of the lung. Our experimental studies have shown the presence of a considerable amount of titanium particles not only in alveolar macrophages but also in hepatocytes (Olmedo et al., 2008b). The accumulation of particles in the liver could compromise liver function as described by Urban et al. (2000). The authors associated the presence of titanium particles in a patient to granulomatous reactions and hepatomegalia. Various studies have reported the presence of macrophages related to failed prostheses, both orthopedic and dental (Adya et al., 2005; Langkamer et al., 1992; Lee et al., 1992; Olmedo et al., 2003; Urban et al., 2002).

As to carcinogenic potential, there are scant reports on the potential development of malignant tumors associated with prosthetic structures in humans (Jacobs et al., 1992). The carcinogenic potential of the released metal ions and the development of associated neoplasias are still controversial issues. Within this context, the need arises to record cases that will contribute to monitor the potential association between tumor development and placing of a prosthetic structure (Apley, 1989; Brien et al., 1990; Goodfellow, 1992). Features such as ionic valence, particle concentration and size and hypersensitivity have been proposed to explain the potential association between malignant transformation and a metallic implant (Jacobs et al., 1992). In the field of Orthopedics in particular, metallic biomaterials are widely used to manufacture surgical materials such as prostheses for hip replacement or internal fixation devices, and surgeons who deal with traumatic, neoplastic, and degenerative disorders of the skeletal muscle system routinely handle these materials. The potential toxicity of some of the metals most frequently employed in the manufacture of orthopedic implants (titanium, aluminum, vanadium, cobalt, chromium, nickel) has been reported (Elinder & Friberg, 1986; Gitelman, 1989; Jacobs et al., 1991; Jandhyala & Hom, 1983; Langard & Norseth; 1986; Sunderman, 1989; Urban et al., 2000; Williams, 1981). Their carcinogenic potential has been evaluated in animal experimental models (Hueper, 1952; Lewis & Sunderman, 1996; Sinibaldi et al., 1976). The development of tumors at the implant site has been described. Most of the tumors were osteosarcomas or fibrosarcomas associated with stainless steel internal fixation devices (Black, 1988a). However, few reports discuss the potential development of malignant tumors associated to prosthetic structures in humans (Jacobs et al., 1992). Several mechanisms potentially involved in implant-related sarcomatous degeneration have been proposed. However, a direct cause-effect relation between the metal and sarcomatous degeneration in patients has not been demonstrated to date (Black, 1988b; Brown et al., 1987; Case et al., 1996; Goodfellow, 1992). As regards titanium specifically, there are reports of neoplasia in association with dental implants, such as squamous cell carcinoma (Gallego et al., 2008) osteosarcoma (McGuff et al., 2008) and plasmacytoma of the mandible (Poggio, 2007). It is of note that TiO_2 was classified by the International Agency for Cancer Research, as possibly carcinogenic to humans (Group 2B) (Baan et al., 2006).

In this regard, our research group reported a case of sarcomatous degeneration in the vicinity of a stainless steel metallic implant, thus adding to the pool of information that may allow determining more accurately the potential toxicity of metallic implants and the risks associated with their use (Olmedo et al., 2007b).

Regarding the use of titanium and zirconium as implantable materials, Thomsen et al. (1997) found that both titanium and zirconium have a positive effect on tissue-material interaction. A previous experimental study conducted at our laboratory on bone tissue response to an implant, showed greater peri-implant bone thickness and volume in bone surrounding zirconium implants as compared to that around titanium implants (Guglielmotti et al., 1999). Zirconium is chemically related to, and has several properties in common with titanium (Thomsen et al., 1997). According to several researchers (Johansson et al., 1994; Sherepo & Red'ko, 2004; Thomsen et al., 1997; Yuanyuan & Yong, 2007), the elasticity, corrosion resistance, and other physico-mechanical properties of zirconium and its alloys make them a suitable material for biomedical implants. Because zirconium offers superior corrosion resistance over most other alloy systems, better behavior in biological environments can be presumed (Stojilovic, 2005). Nevertheless, it is not widely used as a clinical material at present (Thomsen et al., 1997), since commercial manufacture of implants from zirconium or its alloys seems to be unfeasible due to the high cost of this material (Sherepo & Red'ko, 2004). The potential uses of zirconium-based materials for prosthetics and dental applications should be strongly considered and further investigated in laboratory and clinical settings.

5. Nanotechnology - nanotoxicology

Nanotoxicology is a field of applied sciences involving the control of matter on an atomic or molecular scale, i.e. between 1 and 100 nanometers. Nanotechnology allows creating materials, devices, and systems by controlling matter on a nanometric scale taking advantage of new phenomena and properties (physical, chemical, and biological) that appear at a nanometric scale (Drexler 1986; Mendonçaa et al., 2008).

The aim of applying the principles of nanotechnology to biomaterials (orthopedics and dentistry) is to create materials than can be applied directly to bone tissue, mimicking the natural nanostructure of human tissues by controlling the surface of the implant at a nanometric scale. This would improve the interaction between the implant surface with ions, biomolecules, and cells, favoring the biocompatibility properties of the bioimplant (Mendonçaa et al., 2008). For example, titanium implants with nanostructured coatings, films, and surfaces that seemingly improve the integration of bone tissue with the surface of the implant (osseointegration) and decrease the risk of implant corrosion are currently being developed. Although nanotechnology and its valuable contributions seek to provide answers to the increasing demands of different areas, it is important to understand that these advances may not only bring great advantages but also problems and health risks that must be carefully analyzed and prevented. Thus, nanoparticles may involve deleterious effects to humans or the environment. The fields that study these effects are nanotoxicology (Oberdörster et al., 2005) and nanoecotoxicology (Kahru & Dubourguier, 2009).

Nanoparticles can enter the body by inhalation, ingestion, injection, and/or through the skin (Oberdörster et al., 2005). In addition, they can generate inside the body as occurs when they are released from the surface of metallic implants and biomedical devices, such as coxofemoral prostheses, grids, plates, screws, and distractors used in surgery (Revell, 2006). Little is known about the effect, biodistribution, and final destination of nanometric particles (between 1 and 100 nanometers) inside the body. Given that nanoparticles have a larger surface area per unit of mass compared to microparticles, they may be more bioreactive and potentially more detrimental to human health. Although micro and nanoparticles can be chemically similar, their particular physico-chemical properties such as size, shape, electric charge, concentration, bioactivity and stability, may cause a different biological response. Analyzing the chemistry involved in the release of nanoparticles from metallic surfaces, their size, the quantity that enter the biological milieu, the site where they are transported to, and the immediate and long-term physico-pathological consequences of these particles is a challenge to nanotoxicology and biocompatibility studies (Fig. 7 A-C).

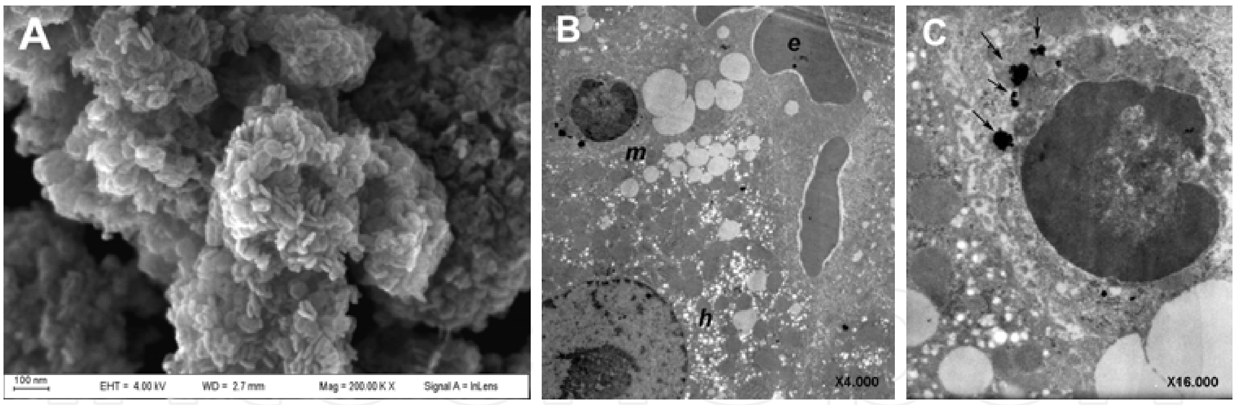

Fig. 7. A) Scanning Electron Microscopy of TiO_2 nanoparticles (10nm). B) Monocyte (*m*) containing nanometric titanium particles (5nm) can be observed in the hepatic sinusoid. (*h*) hepatocyte, (*e*) erythrocyte. X4000. C) Higher magnification allows identifying particles clustered close to the nucleus (→). X16000

6. Conclusions

No metal or alloy is completely inert *in vivo*. Whether noble or passivated, all metals will suffer a slow removal of ions from the surface, largely because of local and temporal variations in microstructure and environment. The potential risk of corrosion and the possible detrimental consequences of corrosion byproducts to tissues are issues of clinical importance.

The biologic effect of corrosion is a public health concern for the community of patients who have a prosthesis (orthopedic and/or dental), since these prostheses remain inside the body over long periods of time.

Evaluation of tissues around metallic devices is important since the presence of ions/particles and their potential local biological effects might affect implant outcome. Corrosion is one of the possible causes of implant failure after initial success. Metal corrosion can affect close contact between the implant and the bone tissue (osseointegration).

The issue of corrosion is not only a local problem since particles resulting from this process could migrate systemically and deposit in target organs. The long term effects of these deposits are yet to be clarified. Mineral elements play a critical role in the physiology and pathology of biological systems. Titanium is a nonessential element; thus, the presence of titanium in the body, titanium biokinetics, and the potential biological effects of titanium are of great interest to researchers.

"In situ" degradation of a metallic implant is an unwanted event since it alters the structural integrity of the implant. Implant manufacturers must attempt to develop methods that reduce the diffusion of metal into the tissues in order to minimize the deleterious effects of corrosion.

We believe further investigation, in particular long-term research, is necessary to advance in the understanding of the factors involved in implant corrosion and establish basic guidelines for their use in clinical implantology. Handling and controlling corrosion of a biomedical implant is essential from a biological, sanitary, metallurgic, economic, and social viewpoint.

Lastly, it is important to highlight that the adverse effects of corrosion described in the present chapter will not invariably occur in all patients with implants since biological response varies among individuals.

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8. References

Abraham, J., Grenón, M., Sánchez, H., Pérez, C. & Valentinuzzi, M. (2006). Titanium Based Implants, Metal Release Study in the Oral Environment. LNLS, Activity report. pp. 1-2, ISSN 1518-0204. Available from URL: http://www.lnls.br/ar2006/PDF/909.pdf

Abramson, S., Alexander, H., Best, S., Bokros, J., Brunski, J., Colas, A., Cooper, S., Curtis, J., Haubold, A., Hensch, L., Hergenrother, R., Hoffman, A., Hubbell, J., Jansen, J., King, M., Kohn, J., Lamba, N., Langer, R., Migliaresi, C., More, R., Peppas, N., Ratner, B.,Visser, S., Von Recum, A., Weinberg, S., Yannas, I. (2004). Classes of Materials Used in Medicine, In: *Biomaterials Science. An Introduction to Materials in Medicine,* B.D. Ratner, A.S. Hoffman, F.J. Schoen & J.E. Lemons, (Eds.), pp. 67-233, Elsevier Academic Press, ISBN: 0-12-582463-7, San Diego, California, USA

Adell, R., Lekholm, U., Rockler, B., Bränemark, P. (1981). A 15-year Study of Osseointegrated Implants in the Treatment of the Edentulous Jaw. *International Journal of Oral and Maxillofacial Surgery,* Vol.10, N°6, pp. 387-416, ISSN 0901-5027

Adya, N., Alam, M., Ravindranath, T., Mubeen, A. & Saluja, B. (2005). Corrosion in Titanium Dental Implants: Literature Review. *Journal of Indian Prosthodontic Society*, Vol.5, N°3, (July), pp. 126-131, ISSN 0972-4052

Alfrey, A. (1989). Physiology of Aluminum in Man, In: *Aluminum and Health: A Critical Review,* H.J. Gitelman, (Ed.), pp. 101-124, Marcel Dekker, ISBN 0824780264, New York, USA

Allen, M., Myer, B., Millet, P. & Rushton, N. (1997). The Effects of Particulate Cobalt, Chromium and Cobalt-chromium Alloy on Human Osteoblast-like Cells in Vitro. *The Journal of Bone and Joint Surgery. British volume, Vol.* 79, N°3, (May), pp. 475-482, ISSN 0301-620X

Anderson, J., Cook, G., Costerton, B., Hanson, S., Hensten-Pettersen, A., Jacobsen, N., Johnson, R., Mitchell, R., Pasmore, M., Schoen, F., Shirtliff, M. & Stoodley, P. (2004). Host Reactions to Biomaterials and Their Evaluation, In: *Biomaterials Science. An Introduction to Materials in Medicine,* B.D. Ratner, A.S. Hoffman, F.J. Schoen & J.E. Lemons, (Eds.), pp. 293-354, Elsevier Academic Press, ISBN: 0-12-582463-7, San Diego, California, USA

Apley, A.. (1989). Editorial. Malignancy and Joint Replacement: the Tip of An Iceberg? *The Journal of Bone and joint Surgery. British volume*, Vol.71, N°1, (January), ISSN 0301-620X

Baan, R., Straif, K., Grosse, Y., Secretan, B., El Ghissassi, F. & Cogliano, V. (2006). Carcinogenicity of Carbon Black, Titanium Dioxide and Talc. *The Lancet Oncology,* Vol.7, N°4, (April), pp. 295-296, ISSN 1470-2045

Bessho K, Iizuka T. (1993). Clinical and animal experiments on stress corrosion of titanium miniplates. *Clinical Materials,* Vol.14, N°3, pp. 223-227, ISSN 0267-6605.

Black, J. (1988a). *Orthopedic Biomaterials in Research and Practice,* Churchill Livingstone, ISBN 0443084858, New York, USA

Black J. (1988b). Editorial. Does Corrosion Matter? *The Journal of Bone and joint Surgery. British volume, Vol.*70, N°4; (August), pp. 517-520. , ISSN 0301-620X

Black, J., Sherk, H., Bonini, J., Rostoker, W., Schajowicz, F. & Galante, J. (1990). Metallosis Associated with a Stable Titanium-alloy Femoral Component in Total Hip Replacement. A Case Report. *The Journal of Bone and Joint Surgery. American volume, Vol.*72, N°1, (January), pp. 126-130, ISSN0021-9355

Brånemark, P., Hansson, B., Adell, R., Breine, U., Lindström, J., Hallén, O. & Ohman, A. (1977). Osseointegrated Implants in the Treatment of the Edentulous Jaw. Experience from a 10-year Period. *Scandinavian Journal of Plastic and Reconstructive Surgery. Supplementum,*Vol.16, pp. 1-132, ISSN 0581-9474

Brien, W., Salvati, E., Heley, J., Bansal, M., Ghelman, B. & Betts, F. (1990). Osteogenic Sarcoma Arising in the Area of a Total Hip Replacement: a Case Report. *The Journal of Bone and Joint Surgery. American volume, Vol.*72, N°7, (August), pp. 1097-1099, ISSN 0021-9355

Brodbeck, W., Macewan, M., Colton, E., Meyerson, H. & Anderson, J.M. (2005). Lymphocytes and the foreign body response: lymphocyte enhancement of macrophage adhesion and fusion. *Journal of Biomedical Materials Research. Part A,* Vol.74, N°2, (August), pp. 222-229, ISSN ISSN 1549-3296

Brown, S., Merrit, K., Farnsworth, L. & Crowe, T. (1987). Biological Significance of Metal Ion Release, In: *Quantitative Characterization and Performance of Porous Implants for Hand Tissue Applications,* J.E. Lemon, (Ed.), pp. 163-181, American Society for Testing and Materials, ISBN 0-8031-0965-2, Philadelphia

Bullough, P. (1994). Metallosis. *The Journal of Bone and joint Surgery. British volume*, Vol.76, N°5, (September), pp. 687-688, ISSN 0301-620X

Cabrini, R., Olmedo, D., Tomasi, V. & Guglielmotti, M. (2002). Microincineration for the Detection of Titanium in Tissue Sections. *Journal of Histotechnology, Vol.*25, N°2, pp. 75-78, ISSN 0147-8885

Cabrini, R., Olmedo, D. & Guglielmotti, M. (2003). A Quantitative Method to Evaluate Corrosion Products in Tissues. *Acta Odontológica Latinoamericana,* Vol.16, N°1-2, pp. 27-33, ISSN 0326-481.

Case, C., Langkamer, V., Howell, R., Webb, J., Standen, G., Palmer, M., Kemp, A., Learmonth, I. (1996). Preliminary Observations on Possible Premalignant Changes in Bone Marrow Adjacent to Worn Total Hip Arthroplasty Implants. *Clinical Orthopaedics and Related Research,* 329 Suppl, (August), pp. 269–279, ISSN 0009-921X

Chaturvedi T. (2009). An Overview of the Corrosion Aspect of Dental Implants (titanium and its alloys). (2009). *Indian Society for Dental Research,* Vol.20, N°1, (January-March), pp.91-98, ISSN 0970-9290

Chowdhury, S., Vohra, Y., Lemons, J., Ueno, M. & Ikeda, J. (2007). Accelerating Aging of Zirconia Femoral Head Implants: Change of Surface Structure and Mechanical Properties. *Journal of Biomedical Materials Research. Part B,* Vol.81, N°2, (May), pp. 486-492, ISSN 1552-4973

Daum, S., Anderson, H., Lilis, R., Lorimer, W., Fischbein, S., Miller, A. & Selikoff, I. (1977). Pulmonary Changes Among Titanium Workers. *Proceedings of the Royal Society of Medicine,* Vol.70, N°4, (April), pp. 31-32, ISSN 0035-9157

Diniz-Freitas, M., García-García, A., Crespo-Abelleira, A., Martins-Carneiro, J., Gándara-Rey, J. (2004). Applications of Exfoliative Cytology in the Diagnosis of Oral Cancer. *Medicina Oral, Patología Oral y Cirugía Bucal,* Vol.9, N°4, (August-October), pp. 355-361, ISSN1137-2834

Dowd, J., Schwendeman, L., Macaulay, W., Doyle, J., Shanbhag, A., Wilson, S., Herndon, J., Rubash, H. (1995). Aseptic Loosening in Uncemented Total Hip Arthroplasty in Canine Model. *Clinical Orthopaedics and Related Research,* N°319, (October), pp. 106-121, ISSN 0009-921X

Drexler, K. (1986). *Engines of Creation: The coming Era of Nanotechnology*, Anchor Books, ISBN 0385199732, New York, USA

Duffó, G., Barreiro, M., Olmedo, D., Crosa, M., Guglielmotti, M. & Cabrini, R. (1999). An experimental model to study implant corrosion. *Acta Odontológica Latinoamericana,* Vol.12, N°1, pp. 3-10, ISSN 0326-4815

Effah, E., Bianco, P. & Ducheyne, P. (1995). Crystal Structure of the Surface of Oxide Layer on Titanium and Its Changes Arising from Immersion. *Journal Biomedical Material Research,* Vol.29, N°1, (January), pp.73-80, ISSN 0021-9304.

Elinder, C. & Friberg, L. (1986). Cobalt, In: *Handbook of the Toxicology of Metals,* L. Friberg, G.F.Nordberg & V.B. Vouk, (Eds.), pp. 211-232, Elsevier, ISBN 0444904433, Amsterdam

Engh, C., Moore, K., Vinh, T. & Engh, G. (1997). Titanium Prosthetic Wear Debris in Remote Bone Marrow. A report of Two Cases. *The Journal of Bone and Joint Surgery. American volume,* Vol.79, N°11, (November), 1721-1725, ISSN 0021-9355

Evrard, L., Waroquier, D. & Parent, D. (2010). Allergies to Dental Metals. Titanium: a New Allergen (in French). *Revue médicale de Bruxelles,* Vol.31, N°1, (January-February), pp. 44-49, ISSN0035-3639

Ferguson, A., Laing, P. & Hodge, E. (1960). The Ionization of Metal Implants in Living Tissues. *The Journal of Bone and Joint Surgery. American volume,* Vol.42, (January), pp. 77-90, ISSN 0021-9355

Ferin, J. & Oberdörster, G. (1985). Biological Effects and Toxicity Assessment of Titanium Dioxides: Anatase and Rutile. *American Industrial Hygiene Association Journal,* Vol.46, N°2, (February), pp. 69-72, ISSN 0002-8894

Flatebø, R., Johannessen, A., Grønningsaeter, A., Bøe, O., Gjerdet, N., Grung, B. & Leknes, K. (2006). Host Response to Titanium Dental Implant Placement Evaluated in a Human Oral Model. *Journal of Periodontology,* Vol.77, N°7, (July), pp.1201-1210, ISSN0022-3492

Gallego, L., Junquera, L., Baladrón, J. & Villarreal, P. (2008). Oral Squamous Cell Carcinoma Associated with Symphyseal Dental Implants: an Unusual Case Report. *The Journal of the American Dental Association,* Vol.139, N°8, (August), pp. 1061-1065, ISSN 0002-8177

Garabrant, D., Fine, L., Oliver, C., Bernstein, L. & Peters, J. (1987). Abnormalities of Pulmonary Function and Pleural Disease Among Titanium Metal Production Workers. *Scandinavian Journal of Work, Environment & Health,* Vol.13, N° 1, pp. 47-51, ISSN 0355-3140

Gitelman, H. (1989). *Aluminum and Health: A Critical Review,* Marcel Dekker, ISBN 0824780264, New York, USA

Goodfellow, J. (1992). Editorial. Malignancy and Joint Replacement. *The Journal of Bone and joint Surgery. British volume,* Vol.74, N°5, (September), pp. 645, ISSN 0301-620X

Gottschling, B., Maronpot, R., Hailey, J., Peddada, S., Moomaw, C., Klaunig, J. & Nyska, A. (2001). The Role of Oxidative Stress in Indium Phosphide-induced Lung Carcinogenesis in Rats. *Toxicological Sciences*, Vol.64, N°1, (November), pp. 28-40, ISSN 1096-6080

Guglielmotti, M. & Cabrini R. (1997). Evaluación Biológica de Implantes Dentales Fracasados. Revista de la Asociación Odontológica Argentina, Vol.85, N°4, pp. 313-317, ISNN 0004-4881

Guglielmotti, M., Renou, S. & Cabrini, R. (1999). A Histomorphometric Study of Tissue Interface by Laminar Implant Test in Rats. *The International Journal of Oral & Maxillofacial Implants,* Vol.14, N°4, (July-August), pp. 565-570, ISSN0882-2786

Guindy, J., Schiel, H., Schmidli, F. & Wirz, J. (2004). Corrosion at The Marginal Gap of Implant-Supported Suprastructures and Implant Failure. *The International Journal of Oral & Maxillofacial Implants,* Vol.19, N°6, (November-December), pp. 826-831, ISSN 0882-2786

Hallab, N., Merrit, K. & Jacobs, J. (2001). Metal Sensitivity in Patients with Orthopaedic Implants. Current Concepts Review. *The Journal of Bone and Joint Surgery. American volume*, Vol.83, N°3, (March), pp. 428-436, ISSN 0021-9355

Henrich, V. & Cox, P. (1994). *The Surface Science of Metal Oxides,* Cambridge University Press, ISNN 0521566878, New York, USA

Hueper, W. (1952). Experimental Studies in Metal Carcinogenesis. I. Nickel Cancers in Rats. *Texas Reports on Biology & Medicine, Vol.*10, N°1, pp. 167-186, ISSN 0040-4675

Jacobs, J., Skipor, A., Urban, J. & Galante, R. (1991). Release and Excretion of Metal in Patients Who Have a Total Hip Replacement Component Made of Titanium Base Alloys. *The Journal of Bone and Joint Surgery. American volume*; Vol.73, N°10, pp. 1475-1486, ISSN 0021-9355

Jacobs, J., Rosenbaum, D., Marshall H., Gitelis S. & Black, J. (1992). Early Sarcomatous Degeneration Near a Cementless Hip Replacement. A Case Report and Review. *The Journal of Bone and joint Surgery. British volume,* Vol.74, N°5, (September), pp. 740-744, ISSN 0301-620X

Jacobs, J., Gilbert, J. & Urban, R. (1998). Current Concepts Review - Corrosion of Metal Orthopaedic Implants. *The Journal of Bone and Joint Surgery. American volume,* Vol.80, N°2, (October), pp. 268-282, ISSN 0021-9355

Jandhyala, B. & Hom G. (1983). Minireview. Physiological and Pharmacological Properties of Vanadium. *Life Sciences,* Vol.33, N°14, (October), pp. 1325-1340, ISSN0024-3205

Javed, F., Al-Hezaimi, K., Almas, K. & Romanos, G. (2011). Is Titanium Sensitivity Associated with Allergic Reactions in Patients with Dental Implants? A Systematic Review. *Clinical Implant Dentistry and Related Research,* (March), doi:10.1111/j.1708-8208.2010.00330.x., ISSN1523-0899

Jiranek, W., Machado, M., Jasty, M., Jevsevar, D., Wolfe, H., Goldring, S., Goldberg, M. & Harris, W. (1993). Production of Cytokines Around Loosened Cemented Acetabular Components. Analysis with Immunochemical Techniques and in Situ Hybridization. *The Journal of Bone and Joint Surgery. American volume,* Vol.75, N°6, (June), :863-879, ISSN 0021-9355

Johansson CB, Wennerberg A, Albrektsson T. (1994). Quantitative Comparison of Screw-Shaped Commercially Pure Titanium and Zirconium Implants in Rabbit Tibia. *Journal of Materials Science. Materials in Medicine,Vol.*5, N°6, (June), pp. 340-344, ISSN 0957-4530

Kahru A. & Dubourguier, H. (2009). From Ecotoxicology to Nanoecotoxicology. *Toxicology,* Vol.269, N°2, (March), pp.105-119, ISSN 0300-483X

Kasemo, B. (1983). Biocompatibility of Titanium Implants: Surface Science Aspects. *The Journal of Prosthetic Dentistry,* Vol. 49, N°6, (June), pp. 832-837, ISSN 0022-3913

Kasemo, B. & Lausmaa, J. (1998). Biomaterial and Implant Surfaces: A Surface Science Approach. *The International Journal of Oral & Maxillofacial Implants,* Vol.3, N°4, (Winter), pp.247-259, ISSN0882-2786

Katou, F., Andohn, N., Motegui, K. & Nagara, H. (1996). Immuno-Inflammatory Responses in the Tissue Adjacent to Titanium Miniplates Used in the Treatment of Mandibular Fractures. *Journal of Cranio-maxillo-facial Surgery*, Vol.24, N°3, (June), pp.155-162, ISSN1010-5182

Kawanishi, S., Oikawa, S., Inoue, S. & Nishino, K. (2002). Distinct Mechanisms of Oxidative DNA Damage Induced by Carcinogenic Nickel Subsulfide and Nickel Oxides. *Environmental Health Perspectives,* Vol.110, N°5, (October), pp. 789-791. 0091-6765

Koppang HS, Roushan A, Srafilzadeh A, Stølen SØ & Koppang R. (2007). Foreign Body Gingival Lesions: Distribution, Morphology, Identification by X-ray Energy Dispersive Analysis and Possible Origin of Foreign Material. *Journal of Rral Pathology and Medicine,* Vol.36, N°3, (March), 161-172, ISSN *0904-2512*

Kumazawa, R., Watari, F., Takashi, N., Tanimura, Y., Uo M. & Totsuka, Y. (2002). Effects of Ti Ions and Particles on Neutrophil Function and Morphology. *Biomaterials,* Vol.23, N°17, pp.3757-3764, ISSN 0142-9612

Laing, P. Compatibility Of Biomaterials. (1973). *The Orthopedic Clinics of North America,* Vol.4, N°2, (April), pp. 249-273, ISSN 0030-5898

Lalor, P., Revell, P., Gray, A., Wright, S., Railton, G. & Freeman, M. (1991). Sensitivity to Titanium. A Cause of Implant Failure? *The Journal of Bone and joint Surgery. British volume, Vol.*73, N°1, (January), pp. 25-28, ISSN 0301-620X

Lang, N., Wilson, T. & Corbet, E. (2000). Biological Complications with Dental Implants: Their Prevention, Diagnosis and Treatment. *Clinical Oral Implants Research,* Vol.11, Suppl 1, pp. 146-155, ISSN 0905-7161

Langard, S. & Norseth, T. (1986). Chromium, In: *Handbook of the Toxicology of Metals,* L. Friberg, G.F.Nordberg & V.B. Vouk, (Eds.), pp. 185-210, Elsevier, ISBN 0444904433, Amsterdam

Langkamer, V., Case C., Heap P., Taylor A., Collins C., Pearse M., & Solomon L. (1992). Systemic Distribution of Wear Debris After Hip Replacement. A Cause for Concern? *The Journal of Bone and joint Surgery. British volume,* Vol.74, N°6, (November), pp. 831-839, ISSN 0301-620X

Lee K, Henry NW, Trochimowicz HJ, Reinhardt CF. (1986). Pulmonary Response to Impaired Lung Clearance in Rats Following Excessive Tio_2 Dust Deposition. *Environmental Research*, Vol.41, N°1, (October), pp. 144-167, ISSN 0013-9351

Lee, J., Salvati E., Betts F., DiCarlo E., Doty S. & Bullough P. (1992). Size of Metallic and Polyethylene Debris Particles in Failed Cemented Total Hip Replacements. *The Journal of Bone and joint Surgery. British volume,* Vol.74, N°3, (May), pp. 380-384, ISSN 0301-620X

Leggett, R. (1989). The Behavior and Chemical Toxicity of U in the Kidney: A Reassessment. *Health Physics,* Vol.57, N°3, (September); pp.365-383, ISSN0017-9078

Lewis, C., & Sunderman F. (1996). Metal Carcinogenesis in Total Joint Arthroplasty. Animal Models. *Clinical Orthopaedics and Related Research,* N°329, (August), pp. 264-268, ISSN 0009-921X

Long, M. & Rack, H. (1998). Titanium Alloys in Total Joint Replacement: A Materials Science Perspective. *Biomaterials,*Vol. 19, N°18, (September), pp. 1621-1639, ISSN 0142-9612

Lothar, P., Weili, L.,& Horst, H. (1992). Effect of Fluoride Prophylactic Agents on Titanium Surfaces. *The International Journal of Oral & Maxillofacial Implants,*Vol.7, N°3, (Fall), pp. 390-394, ISSN0882-2786

Lu J, Descamps M, Dejou J, Koubi G, Hardouin P, Lemaitre J, Proust JP. (2002). The Biodegradation Mechanism of Calcium Phosphate Biomaterials in Bone. *Journal of Biomedical Materials Research. Part A,* Vol.63, N°4, pp. 408-412, ISSN1549-3296

Lucas, L. & Lemons, J. (1992). Biodegradation of Restorative Metallic Systems. *Advances in Dental Research,* Vol.6, (September), pp.32-37, ISSN 0895-9374Manicone, P., Rossi Iommetti, P. & Raffaelli, L. (2007). An Overview of Zirconia Ceramics: Basic Properties and Clinical Applications. *Journal of Dentistry, Vol.*35, N°11, (November), pp. 819-826, 0300-5712

Matthew, I., Frame, J., Browne, R. & Millar, B. (1996). In Vivo Surface Analysis of Titanium and Stainless Steel Miniplates and Screws. *International Journal of Oral and Maxillofacial Surgery, Vol.*25, N°6, (December), pp. 463-468, ISSN0901-5027

Matthew, I. & Frame, J. (1998). Allergic Responses to Titanium. *Journal of Oral and Maxillofacial Surgery, Vol.*56, N°2, (December), pp.1466-1467, ISSN 0278-2391

Maziere, C., Floret, S., Santus, R., Morliere, P., Marcheux, V. & Maziere, J. (2003). Impairment of The EGF Signaling Pathway by the Oxidative Stress Generated with UVA. *Free Radical Biology & Medicine,*Vol.34, N°6, (March), pp. 629-636. ISSN 0891-5849

McGuff, H., Heim-Hall, J., Holsinger, F., Jones, A., O'Dell, D. & Hafemeister, A. (2008). Maxillary Osteosarcoma Associated with A Dental Implant: Report of a Case and Review of the Literature Regarding Implant-Related Sarcomas. *The Journal of the American Dental Association,* Vol.139, N°8, pp. 1052-1059, ISSN 0002-8177

Meachim, G. & Williams, D. Changes In Nonosseous Tissue Adjacent to Titanium Implants. (1973). *Journal of Biomedical Materials Research, V*ol.7, N°6, (November), pp. 555-572, ISSN 0021-9304 (Print) 1097-4636

Meffert, R., Langer, B. & Fritz, M. (1992). Dental Implants: A Review. *Journal of Periodontology,* Vol.63, N°11, (November), pp. 859-870, ISSN0022-3492

Mendonçaa, G., Mendonçaa, D., Aragãoa, F. & Cooperb, L. (2008). Advancing Dental Implant Surface Technology - From Micron- to Nanotopography. *Biomaterials,* Vol.29, N°28, (October), 3822-3835, ISSN 0142-9612

Merritt, K., Brown, S. & Sharkey, N. (1984). The Binding of Metal Salts and Corrosion Products to Cells and Proteins In Vitro. *Journal of Biomedical Materials Research. Part A,* Vol.18, N°9, (November-December), pp. 1005-1015.

Moberg LE, Nordenram Å, Kjellman O. (1989). Metal Release from Plates Used in Jaw Fracture Treatment. A Pilot Study. *International Journal of Oral and Maxillofacial Surgery*, Vol.18, N°5, (October), pp. 311-314, ISSN 0901-5027

Moran, C., Mullick, F., Ishak, K., Johnson, F. & Hummer, W. (1991). Identification of Titanium in Human Tissues: Probable Role In Pathologic Processes. *Human Pathology,* Vol.22, N°5, (May), pp. 450-454, ISSN 0046-8177

Nalli, G., Verdú, S., Paparella, M., Olmedo, D & Cabrini, R. (2009). Exfoliative Cytology and Titanium Dental Implants. A Preliminary Study. *Journal of Dental Research* (in press)

Newman, M. & Flemming, T. (1988). Periodontal Considerations of Implants and Implant Associated Microbiota. *Journal of Dental Education, Vol.*52, N°12, (December), pp. 737-744, ISSN0022-0337

Nikolopoulou, F. Saliva and Dental Implants. (2006). *Implant Dentistry,* Vol.15, N°4, (December), pp. 372-376. ISSN 1056 6163

Oberdörster, G., Oberdörster, E. & Oberdörster J. (2005). Nanotoxicology: An Emerging Discipline Evolving from Studies of Ultrafine Particles. *Environmental Health Perspectives,*Vol.113, N°7, (July), pp. 823-839, ISSN 0091-6765

Olmedo, D., Guglielmotti, M., Cabrini, R. (2002). An Experimental Study of the Dissemination of Titanium and Zirconium in The Body. *Journal of Materials Science. Materials in Medicine, Vol.*13, N°8, (August) 793-796, ISSN 0957-4530

Olmedo, D., Fernández, M., Guglielmotti, M. & Cabrini, R. (2003a). Macrophages Related to Dental Implant Failure. *Implant Dentistry*; Vol.12; N°1, pp.75-80, ISSN 1056-6163

Olmedo, D., Tasat, D., Guglielmotti, M. & Cabrini, R. (2003b). Titanium Transport Through the Blood Stream. An Experimental Study In Rats. *Journal of Materials Science. Materials in Medicine, Vol.*14, N°12, pp. 1099-1103, ISSN 0957-4530

Olmedo, D., Tasat, D., Guglielmotti, M. & Cabrini, R. (2005). Effect of Titanium Dioxide on The Oxidative Metabolism of Alveolar Macrophages: An Experimental Study In Rats. *Journal of Biomedical Materials Research. Part A,*Vol.73, N°2, (May), pp. 142-149, ISSN1549-3296

Olmedo, D., Paparella, M., Brandizzi, D., Spielberg, M. & Cabrini. (2007a). R. Response of Oral Mucosa Associated to Titanium Implants. *Journal of Dental Research 86 (Spec Iss B):* 0083. Available from URLhttp://iadr.confex.com/iadr/arg07/preliminaryprogram/abstract_114433.htm

Olmedo, D., Michanié, E., Olvi, L., Santini-Araujo, E. & Cabrini, R. (2007b). Malignant Fibrous Histiocytoma Associated to Coxofemoral Arthrodesis. *Tumori,* Vol.93, N°5, (September-October), pp. 504-507, ISSN 0300-8916

Olmedo, D., Tasat, D., Evelson, P., Guglielmotti, M. & Cabrini, R. (2008a). Biological Response of Tissues with Macrophagic Activity to Titanium Dioxide. *Journal of*

*Biomedical Materials Research. Part A, Vol.*84, N°4, (March), pp. 1087-1093, ISSN1549-3296

Olmedo, D., Tasat, D., Evelson, P., Guglielmotti, M. & Cabrini, R. (2008b). Biodistribution of Titanium Dioxide from Biologic Compartments. *Journal of Materials Science. Materials in Medicine,* Vol.19, N°9, (September), pp. 3049-3056, ISSN 0957-4530

Olmedo, D., Duffó, G., Cabrini, R. & Guglielmotti, M. (2008c). Local Effect of Titanium Implant Corrosion: An Experimental Study in Rats. *International Journal of Oral and Maxillofacial Surgery*, Vol.37, N°11, (November), pp.1032-1038, ISSN 0901-5027

Olmedo, D., Tasat, D., Duffó, G., Guglielmotti, M. & Cabrini, R. (2009). The Issue of Corrosion in Dental Implants: A Review. *Acta Odontológica Latinoamericana,* Vol.22, N°1, pp. 3-9, ISSN 0326-4815

Olmedo, D., Paparella, M., Brandizzi, D. & Cabrini, R. (2010). Reactive Lesions of Peri-Implant Mucosa Associated with Titanium Dental Implants: A Report Of 2 Cases. *International Journal of Oral and Maxillofacial Surgery,* Vol.39, N°5, (May), pp. 503-507, ISSN 0901-5027

Olmedo, D., Tasat, D., Evelson, P., Rebagliatti, R., Guglielmotti, M. & Cabrini, R. (2011). In Vivo Comparative Biokinetics and Biocompatibility of Titanium and Zirconium Microparticles. *Journal of Biomedical Materials Research. Part A,* Vol.98, N°4, (September), pp. 604-613, ISSN 1549-3296

Poggio, C. (2007). Plasmacytoma of the Mandible Associated with a Dental Implant Failure: A Clinical Report. *Clinical Oral Implants Research,* Vol.18, N°4, (August), pp. 540-543, ISSN 0905-7161

Ratner, B., Hoffman, A., Schoen, F. & Lemons, J. (2004). Biomaterials Science: A Multidisciplinary Endeavor, In: *Biomaterials Science. An Introduction to Materials in Medicine,* B.D. Ratner, A.S. Hoffman, F.J. Schoen & J.E. Lemons, (Eds.), pp. 1-9, Elsevier Academic Press, ISBN: 0-12-582463-7, San Diego, California, USA

Revell, P. (2006). The Biological Effects of Nanoparticles. *Nanotechnology Perceptions,* Vol.2, N°3, pp. 283-298, ISSN 1660-6795

Rosenberg, A., Grätz, K. & Sailer, H. (1993). Should Titanium Miniplates Be Removed After Bone Healing is Complete? *International Journal of Oral and Maxillofacial Surgery,* Vol.22, N°3, (June), pp.185-188, ISSN 0901-5027

Schliephake, H., Lehmann, H., Kunz, U., Schmelzeisen & R. (1993). Ultrastructural Findings in Soft Tissues Adjacent to Titanium Plates Used in Jaw Fracture Treatment. *International Journal of Oral and Maxillofacial Surgery, Vol.*22, N°1, (February), pp. 20-25, ISSN0901-5027

Sherepo, K. & Red'ko, I. (2004). Use of Zirconium-Based and Zirconium-Coated Implants in Traumatology and Orthopedics. *Biomedical Engineering,* Vol.38, N°2, (March), 77-79, ISSN 1475-925X

Sicilia, A., Cuesta, S., Coma, G., Arregui, I., Guisasola, C., Ruiz, E. & Maestro, A. (2008). Titanium Allergy in Dental Implant Patients: A Clinical Study on 1500 Consecutive Patients. *Clinical Oral Implants Research,* Vol.19,N°8, (August), pp. 823-835, ISSN 0905-7161

Siirilä, H. & Könönen, M. (1991). The Effect Of Oral Topical Fluorides On The Surface of Commercially Pure Titanium. *Journal of Oral & Maxillofacial Implants,* Vol.6, N°1, (Spring), pp. 50-54, ISSN0882-2786

Sinibaldi, K., Rosen, H., Liu, S. & DeAngelis, M. (1976). Tumors Associated with Metallic Implants in Animals. *Clinical Orthopaedics and Related Research,* N°118, (July-August), 257-266., ISSN 0009-921X

Solheim, E., Sudmann, B., Bang, G. & Sudmann, E. (2000). Biocompatibility and Effect on Osteogenesis of Poly(Ortho Ester) Compared to Poly(DL-Lactic Acid). *Journal of Biomedical Materials Research. Part A,* (February), Vol.49, N°2, pp. 257-263, ISSN 1549-3296

Sollazzo, V., Palmieri, A., Pezzetti, F., Bignozzi, C., Argazzi, R., Massari, L., Brunelli, G &, Carinci, F. (2007). Genetic Effect of Zirconium Oxide Coating on Osteoblast-Like Cells. *Journal of Biomedical Materials Research. Part B, Vol.*84, N°2, (February), pp.550-558, ISSN 1552-4973

Stojilovic, N., Bender, E. & Ramsier, R. (2005). Surface Chemistry Of Zirconium. *Progress in Surface Science,* Vol. 78, N°3, pp. 101-184, ISSN 0079-6816

Sul, Y., Johansson, C., Jeong, K., Roser, K., Wennerberg, A. & Albrektsson, T. (2001). Oxidized Implants and Their Influence on Their Bone Response. *Journal of Materials Science. Materials in Medicine*, Vol.12, N°10-12, (October-December), pp. 1025-1031, ISSN 0957-4530

Sunderman, F. (1989). A Pilgrimage Into The Archives of Nickel Toxicology. *Annals of Clinical and Laboratory Science,* Vol.19, N°1, (January-February), pp. 1-16, ISSN 0091-7370

Tagger Green, N., Machtei, E., Horwitz, J. & Peled, M. (2002). Fracture of Dental Implants: Literature Review And Report Of A Case. *Implant Dentistry*; Vol. 11, N°2, pp. 137-143, ISSN 1056-6163

Takebe J, Champagne CM, Offenbacher S, Ishibashi K, Cooper LF. (2003). Titanium Surface Topography Alters Cell Shape and Modulates Bone Morphogenetic Protein 2 Expression In The J774A.1 Macrophage Cell Line. *Journal of Biomedical Materials Research. Part A,* Vol.64, N°2, (February), pp. 207-216, ISSN 1549-3296

Textor, M., Sittig, C., Frauchiger, V., Tosatti, S. & Brunette, D. (2001). Properties and Biological Significance of Natural Oxide Films on Titanium and Its Alloys, In: *Titanium in Medicine,* D.M. Brunette, P. Tengvall, M. Textor, P. Thomsen, (Eds.), pp. 171-230, Springer-Verlag, ISBN 3540669361, Berlin, Germany

Thomsen, P., Larsson, C., Ericson, L., Sennerby, L., Lausmaa, J. & Kasemo, B. (1997). Structure of The Interface Between Rabbit Cortical Bone and Implants Of Gold, Zirconium And Titanium. *Journal of Materials Science. Materials in Medicine,* Vol.8, N°11, pp. 653-665, ISSN 0957-4530

Torgersen, S., Gjedet, N., Erichsen, E. & Bang, G. (1995). Metal Particles and Tissue Changes Adjacent to Miniplates. A Retrieval Study. *Acta odontologica Scandinavica,* Vol.53, N°2, (April), pp. 65-71, ISSN0001-6357

Urban, R., Jacobs, J., Gilbert, J. & Galante, J. (1994). Migration of Corrosion Products from Modular Hip Prostheses. Particle Microanalysis and Histopathological Findings. *The Journal of Bone and Joint Surgery. American volume,* Vol.76, N°9, (September), pp. 1345-1359, ISSN 0021-9355

Urban, R., Jacobs, J., Tomlinson, M., Gavrilovic, J., Black, J. & Peoc´h, M. (2000). Dissemination of Wear Particles to The Liver, Spleen, and Abdominal Lymph Nodes of Patients with Hip or Knee Replacement. *The Journal of Bone and Joint Surgery. American volume,Vol.*82, N°4, (April), pp. 457-476, ISSN 0021-9355

Williams, D. (1981). Biological Effects of Titanium, In: *Systemic Aspects of Biocompatibility,* D.F. Williams, (Ed.), pp. 169-177, CRC Press, ISBN 0849366216, Boca Ratón, Florida, USA

Williams, D. (1982). Corrosion of Orthopaedic Implants, In: *Biocompatibility of Orthopaedic Implants,* D.F. Williams, (Ed.), pp. 197-229, CRC Press, ISBN 0849366135, Boca Ratón, Florida, USA

Williams, D. (1987). Definitions in Biomaterials, *Proceedings of a Consensus Conference of the European Society for Biomaterials*, ISBN 0444428585, Chester, England, March 3-5, 1986

Woodman, J., Black, J. & Jimenez, S. (1984a). Isolation of Serum Protein Organometallic Corrosion Products from 316LSS And HS-21 in Vitro and in Vivo. *The Journal of Bone and Joint Surgery. American volume,* Vol.18, N°1, (January), pp. 99-114, ISSN 0021-9355

Woodman, J., Jacobs, J., Galante, J. & Urban, R. (1984b). Metal Ions Release from Titanium-Based Prosthetic Segmental Replacements of Long Bones in Baboons: A Long-Term Study. *Journal of Orthopaedic Research*, Vol.1, N°4, pp. 421-430, ISSN *0736-0266*

Xia, Z. & Triffitt J. (2006). A Review on Macrophage Responses to Biomaterials. *Biomedical Materials,* Vol.1, N°1; pp. 1-9, (March), ISSN 1748-6041

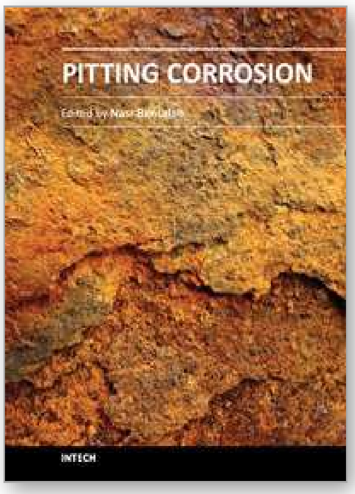
Yang, J. & Merrit, K. (1994). Detection of Antibodies Against Corrosion Products in Patients After Co-Cr Total Joint Replacements. *Journal of Biomedical Materials Research. Part A,* Vol.28, N°11, (November), 1249-1258., ISSN1549-3296

Young-Kyun, K., Hwan-Ho, Y. & Seung-Cheul, L. (1997). Tissue Response to Titanium Plates: A Transmitted Electron Microscopic Study. *Journal of Oral and Maxillofacial Surgery,* Vol.55, N°4, (April), pp. 322-326, ISSN 0278-2391

Yuanyuan, Y. & Yong, H. (2007). Structure and Bioactivity of Micro-arc Oxidized Zirconia Films. *Surface and Coatings Technology, Vol.*201, N°9, (February), pp. 5692-5695, ISSN.

Zaffe, D., Bertoldi, C., Consolo & U. (2003). Element Release from Titanium Devices Used in Oral and Maxillofacial Surgery. *Biomaterials, Vol.*24, N°6, (March), pp. 1093-1099, ISSN 0142-9612

Zirconium. *Mineral Information Institute.* 2009. Available from URL: http://www.mii.org/Minerals/photozircon.html



Pitting Corrosion

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Taking into account that corrosion is costly and dangerous phenomenon, it becomes obvious that people engaged in the design and the maintenance of structures and equipment, should have a basic understanding of localized corrosion processes. The Editor hopes that this book will be helpful for researchers in conducting investigations in the field of localized corrosion, as well as for engineers encountering pitting and crevice corrosion, by providing some basic information concerning the causes, prevention, and control of pitting corrosion.

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