

# Fix, Heal, and Disappear: A New Approach to Using Metals in the Human Body

by Barbara A. Shaw, Elizabeth Sikora, and Sanna Virtanen

An interesting trend in the development of modern materials for biomedical applications, especially from a corrosion standpoint, is bioabsorbability. The idea that once implanted, the device would stay in the human body only for the time it takes to “fix” the problem and then quietly dissolve (corrode) away is indeed fascinating. With this approach, corrosion becomes a desirable materials property.

As the average age of patients receiving implants is decreasing (at least in part due to sports and war injuries) the concerns associated with permanent implants becomes more serious. As a result, bioabsorbable, metallic implants provide a solution for a number of the problems associated with permanent metallic implants: restenosis, thrombosis, permanent physical irritation, and inability to adapt to growth and changes in human body. Also, the issue of long-term release of metallic ions and/or particles through the corrosion or wear process that may eventually result in loss of an implant’s biocompatibility is removed with a bioabsorbable implant. The need for a second surgical procedure to remove the temporary metallic parts after the tissue has sufficiently healed; can also be avoided with a bioabsorbable implant; therefore, lowering overall health care costs.

This article briefly highlights some of the electrochemical corrosion research being conducted on resorbable, magnesium-based alloys (containing Y) for possible use in human bioimplants at two independent university research groups: one in the U.S. (producing and characterizing new alloys made via vapor deposition methods) and one in Europe (evaluating alloys produced via conventional, commercial methods).

## Background

*Mg as a new bioabsorbable biomaterial.*—Quite recently, magnesium and its alloys are being reconsidered for use as biomaterials suitable for: (1) degradable bone implants with high initial stability<sup>1</sup> and (2) bioabsorbable cardiovascular stents.<sup>2</sup> The choice of magnesium as a biodegradable material for implants is fortunate because:

- Mg dissolution is highly unlikely to have adverse side effects since magnesium is the fourth most plentiful cation in the human body.

- Mg takes part in many metabolic reactions and biological systems, including involvement in the formation of biological crystal apatite<sup>3</sup> (which is important for metallic bone implants). It is also a co-factor for many enzymes and stabilizes the structures of DNA and RNA.<sup>4</sup>
- Mg can be beneficial from a physiological standpoint, since magnesium deficiencies in the human body significantly contribute to cardiovascular disease.<sup>5</sup> It has also been found that low serum Mg levels are associated with an increased risk for neurological events in patients with symptomatic peripheral artery disease.<sup>6</sup>

Degradable magnesium alloy implants were initially introduced into orthopedic and trauma surgery in the 1930s;<sup>7-9</sup> however, because of inappropriately high corrosion rates due to large amounts of impurities in these early alloys, their use was discontinued shortly after their introduction. Today’s magnesium alloys are superior to those produced in the 1930s and new production methods (like vapor deposition) allow the production of Mg alloys with nonequilibrium compositions and tailored properties which can result in even lower corrosion rates and specialized microfeatures allowing for characteristics such as drug-elution.

The modes and rates of deterioration of the magnesium implants are governed by the alloy composition, structure, and processing. Magnesium is a very reactive metal and its alloys are known for their rapid corrosion in aqueous environments. Usually an implant only needs to remain in place for as long as required for the damaged tissue to heal (typically from a few days to a few weeks for cardiovascular applications); a bone implant needs to remain in the body and maintain mechanical integrity until the bone tissue heals and is replaced by natural tissue (typically from 12 to 18 weeks). As a result, magnesium alloys need to be initially corrosion-resistant in an aggressive, chloride-containing environment like the human body and then corrode in a very controlled, uniform fashion with the release of very fine dissolution products. It is most important that the alloying elements not be detrimental to the human body.

*Orthopedic applications.*—Magnesium and Mg alloys have much higher tensile yield strengths and modulus values than degradable polymeric implant materials, like HA/PLLA 50/50.<sup>10</sup> Mg and its alloys have elastic modulus, compressive yield strengths and density values that are closer to those of natural bone than any other commonly used metallic implant.<sup>11</sup> In Germany, Witte, *et al.*<sup>12</sup> investigated the degradation mechanisms at the bone-implant interfaces of different magnesium alloys in guinea pig femurs. Their results showed that the metallic implants degraded according to the chemical composition of the alloys, and they noted a significantly greater bone mass and a higher mineral apposition rate around the degrading magnesium implants when compared to degradable polymer implants (which served as a control). Recently, the same research group attempted to use porous scaffolds made of a commercial magnesium alloy (AZ91D) as a temporary replacement for the subchondral bone plate for cartilage repair.<sup>13-15</sup> The scaffolds were implanted into the right knee of New Zealand white rabbits and the inflammatory response to their rapid degradation was examined after three and six months. The results confirmed good biocompatibility of the magnesium alloy with no significant harm to neighboring tissue. However, the degradation process was very fast and even if the rapid degradation seems to be vital for optimized nutrition of the regenerating cartilage, the high initial corrosion rates must be controlled to allow sufficient cartilage regeneration. In addition, cytocompatibility tests revealed that osteoblasts and human bone derived cells adhere, proliferate, and survive on the corroding surface of AZ91D; whereas, the macrophages showed significant reduction in cell viability, which was explained by the presence of aluminum ions.

*Cardiac Applications.*—Mg alloys are also attractive materials for cardiovascular stents.<sup>16-18</sup> Currently, problems with permanent, stainless steel stents include: restenosis, difficulties with MRI imaging, limitations on further cardiac interventions due to the presence of numerous permanent stents already in the artery (“full metal jacket” limitations), inability to help infants and small children whose growing arteries need a stent that either grows with the artery or disappears, and concerns about long-term biologic

interactions with metal and/or polymers and arterial walls. In Europe, magnesium stents have already been implanted into the coronary arteries in 63 patients (PROGRESS-AMS study)<sup>19</sup>. While these initial implantations have proven the feasibility of the approach, the rate of restenosis was higher than expected and additional research is necessary.

### Corrosion Behavior of Conventional Mg Alloys in (Simulated) Biological Environments

Corrosion behavior of commercial Mg alloys has been studied in typical environments the alloys may encounter in different applications (for instance NaCl solutions). General information on critical issues in the corrosion behavior of Mg alloys can be found in references.<sup>20,21</sup> Upon exposure to human body the alloy surface not only encounters a simple saline solution (from an inorganic chemistry viewpoint NaCl and other salts are present), but also many biomolecules (*e.g.*, different proteins) and cells. Therefore, it is not surprising that the corrosion behavior observed in the laboratory and *in vivo* for biomaterials are often different. A perfect simulation of the complex interactions between the material surface, corrosion products and all chemical and biological species involved in the *in vivo* case is hardly possible in the laboratory. In the exploratory field of using Mg alloys as biomaterials, the *in vivo* corrosion has of course been far less studied than for more traditional biomaterials. In the literature, a comparison of the *in vitro* and *in vivo* corrosion of two magnesium alloys can be found.<sup>22</sup> The *in vivo* corrosion of intramedullary rods in guinea pig femora was followed by synchrotron-assisted microtomography. The study reports *in vivo* corrosion rates, which are about four orders on magnitude lower than the corrosion rates determined by immersion or electrochemical testing in the laboratory according to ASTM norms. The *in vitro* testing was carried out in chloride solutions or in borate buffer, and, therefore, is not a very good simulation for body fluids. Nevertheless, such a huge difference in the corrosion rates is difficult to explain, even considering different chemistries of the environment, possible inhibiting action by proteins, or other specifics of the *in vivo* case.

For Mg and Mg alloys, systematic studies on the different complex interactions between materials, proteins, and cells are in the very early stage of research. For instance, the effect of proteins on the corrosion of

Mg alloys has not been systematically studied. A recent paper reports that the presence of albumin improves the corrosion behavior of Mg and its alloys.<sup>23</sup> Also, preliminary work indicated that addition of albumin in simulated body fluids can significantly influence the corrosion behavior of Mg alloys; but not only inhibition effects were observed. Details and mechanisms of this behavior still need to be elucidated. *In vitro* cell culture testing on corroding Mg surfaces is not a very easy task, as the relatively fast corrosion of Mg in the cell culture medium is related to H<sub>2</sub>-gas formation, pH increase, and a very dynamic surface structure—all these factors hamper the adhesion of cells on the surface. However, a report can be found in the literature indicating no signs of cellular lysis and no inhibitory effect on cell growth due to the presence of pure Mg samples in mice marrow cell cultures.<sup>24</sup>

Even without considering the effect of the biological species on the corrosion behavior, recent research demonstrates that the corrosion behavior of Mg alloys in simulated body fluids can very drastically differ from findings in simple saline solutions.<sup>25,26</sup> A study of a commercial Mg alloy (WE 43) indicates that a major influencing factor comparing the corrosion behavior in NaCl vs. simulated body fluids is the buffering of the SBF solutions.<sup>27</sup> In non-buffered NaCl, corrosion of Mg leads to fast surface alkalization; therefore the corrosion rate decreases as a function of time, a stable Mg(OH)<sub>2</sub> is forming on the surface. However, in the presence of chlorides, no true passivity is observed, and the dissolution proceeds in an uneven manner. In electrolytes buffered to pH 7.4, the corrosion rates are higher than in non-buffered NaCl solution. This is due to the fact that the surface stabilizing pH-increase is hampered by buffering in the neutral range. In simulated body fluids, with phosphates, carbonates and Ca<sup>2+</sup> ions in the solution, the surface becomes covered by an amorphous carbonated, hydrated (Ca,Mg)-phosphate layer, but this layer offers very little corrosion protection. However, it is noteworthy that in all buffered solutions the corrosion rate is a very steady function of the immersion time; this in contrast to the behavior in NaCl solution, where strong fluctuations in the corrosion behavior as a function of time were observed. How far these findings can be transferred to understand biodegradation of Mg base implants, still remains an open question.

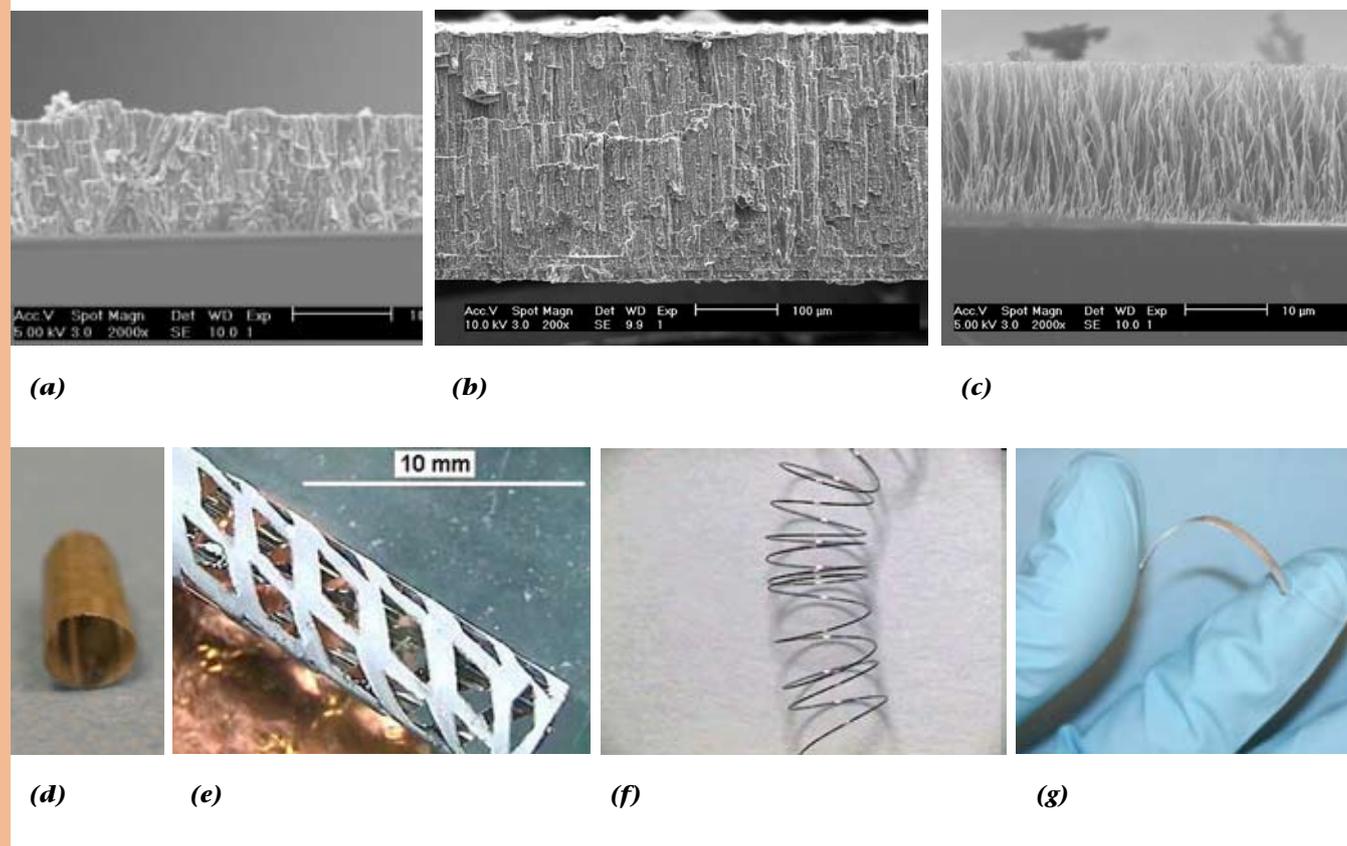
Currently, the interest in the corrosion behavior of Mg alloys from the viewpoint of applications in medicine is increasing. Also, different types of surface treatments are being explored, and novel alloys are being developed, to control the dissolution rates in a desired range. The challenge

in the field of alloy development is not easy in this case, as not only the usual metallurgical considerations have to be taken into account, but moreover the biocompatibility of the alloying elements should be considered. Therefore, a promising route to progress in this field is to use novel techniques for alloy development.

*Vapor deposited Mg-based alloys.*—Nonequilibrium processing via vapor deposition allows one to chemically and physically tailor an alloy over a range of length scales (ranging from nano to micro) while still maintaining a solid solution. This approach allows one to control the corrosion characteristics (dissolution profiles) of the material better than can be achieved with conventional processing methods. This freedom to alter the properties of the material (like adjusting its dissolution kinetics) can be exploited in other ways that are useful for biomaterials (*e.g.* drug eluting bone plates or stents and implantable carriers of chemotherapeutic drugs to tumor sites). In addition, there is also the flexibility to alter the porosity or pattern the metal on a micro or nano scale as a function of thickness of the material. Such an open-cellular surface structure would permit easy transport of fluids and compounds and the structure of these openings could have their micro and nanostructures optimized to alter kinetics of drug release. Also alternation of surface morphology will permit one to create different surface characteristics (hydrophilic or hydrophobic properties) of the metal without a need for the presence of polymers which could be harmful to human body. Extremely fine grained alloys can be produced alleviating the chunking problem to which Mg alloys are susceptible.

Figure 1 shows micrographs of some the vapor deposited alloys produced to date. These deposits have been in the form of thin (1a and 1c) and thick (1b) coatings on flat substrates (such as glass, oxidized Si wafers, metals, and plastics); coatings on round wire substrates (1f); free-standing planar sheets (1g); and seamless tubular specimens (1d and 1e). The deposits have ranged from fully dense films (1a and 1b) to a porous array of nanowires (1c).

To date the most promising vapor deposited Mg-based alloys (produced via sputter or electron beam physical vapor deposition) contain alloying additions of Y and Ti. Their electrochemical behavior has been characterized in Hanks' solution (HBSS) at 37°C. Figure 2 presents corrosion rates (via polarization resistance) for several of the Mg-Y-Ti vapor deposited alloys (A, B, C, and D in Fig. 2) compared to some commercially available Mg alloys: WE 43, EV31, and bulk Mg. WE 43 is a commercial Mg alloy containing Y, Nd, Zr, (and other rare earths) it is among the most corrosion-resistant commercial Mg



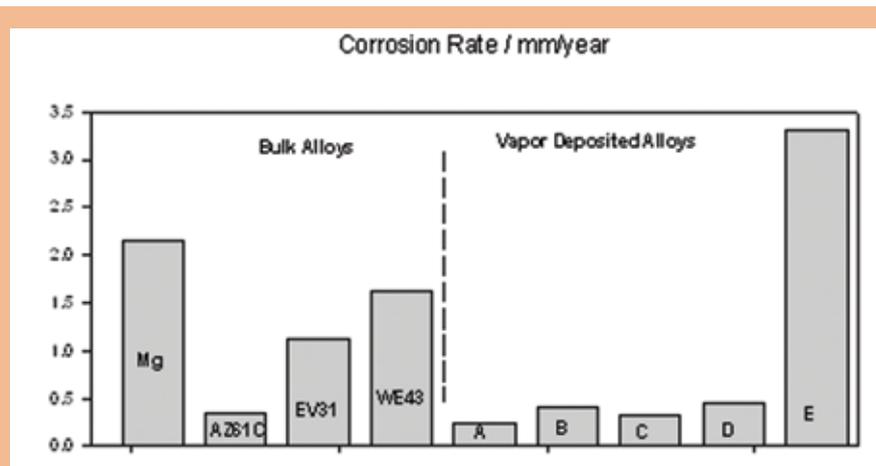
**Fig. 1.** Several forms of vapor deposited alloys produced to-date: (a) dense Mg alloy thin-film (10  $\mu\text{m}$ ) coating, (b) dense Mg alloy thick-film (400  $\mu\text{m}$ ) coating, (c) structured porous array of Mg nanowires, (d) seamless Mg tube, (e) seamless, patterned Mg tube, (f) vapor deposited coating on wire, and (g) a free-standing strip of thick, vapor deposited Mg alloy upon bending.

alloys. WE 43 and another Mg alloy EV 31 (with Nd, Gd, and rare earths) were used as the primary control materials. WE 43 and EV 31 are not currently used for bone plates and screws, but there is interest in Europe in using (at least WE 43) for orthopedic applications. The electrochemical measurements show that all Mg alloys are very active, displaying corrosion potentials which range between  $-1.51 V_{\text{SCE}}$  (thin film alloy C) and  $-1.59 V_{\text{SCE}}$  (conventional alloy WE 43). In general, the vapor deposited thin-films exhibit slightly higher potentials. The difference between the thin-film Mg alloys and conventional ones is more clearly seen when comparing their corrosion rates. The rates, calculated from polarization resistance measurements, are presented in Fig. 2. By varying not only the composition, but to some extent the structure and morphology of the alloy (alloy E), one can obtain alloys with a significant range in their dissolution rates. Among commercial alloys the lowest corrosion rate is shown by AZ61C; however, the presence of Al is usually not desired from a biological perspective.

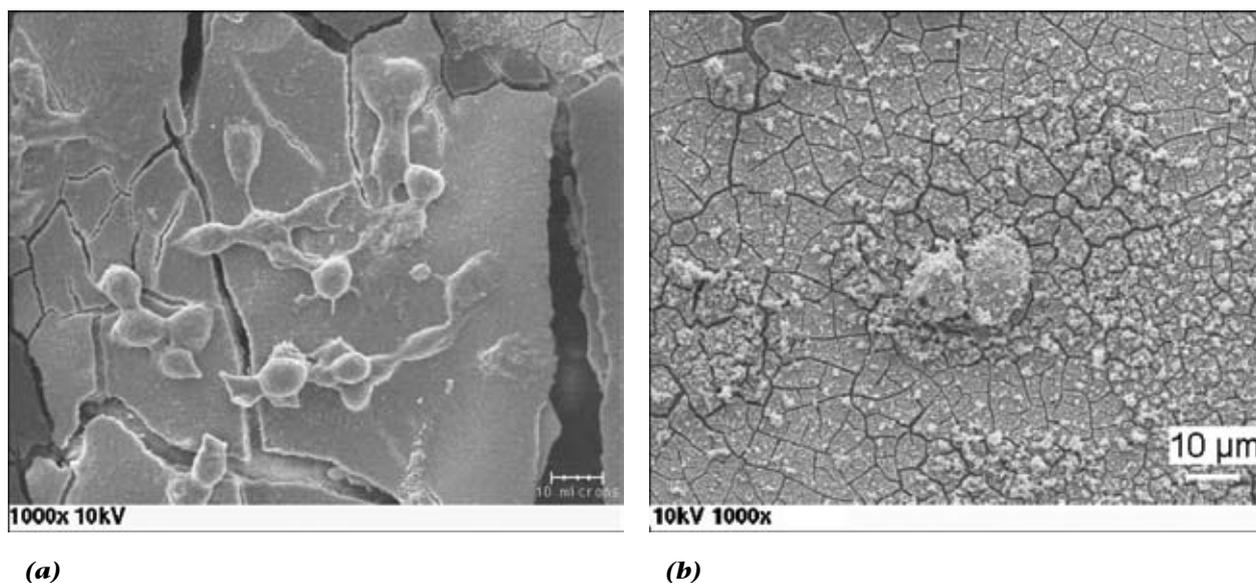
Quite recently, thick (up to 500  $\mu\text{m}$ ) magnesium alloys deposits (presented in Fig. 1b) have been produced. The

alloys showed a great deal of ductility (flexibility) as illustrated in Fig. 1g where the alloy is shown being bent up to 100 degrees. This alloy's elastic modulus, determined from a three-point bending test, was approximately  $35 \times 10^9 \text{ GPa}$ ; this value is very close to the one obtained for natural bone (3-30 GPa)<sup>1</sup> and lower than that for commercial magnesium alloys. The corrosion rate for this thick unoptimized alloy was

measured immediately after immersion in HBSS at 37°C and found to be slightly higher than that of wrought WE 43; however, the corrosion rate decreased after one hour reaching the same value as wrought WE 43. More importantly, the EDPVD alloy has a much lower Y content which is significant since the influence of Y's prolonged presence in the human body is not known.



**Fig. 2.** The corrosion rates calculated from linear polarization measurements for bulk and thin-film Mg-based alloys in HBSS at 37°C.



**Fig. 3.** Cell culture exposure (a) live cells (elongated) on vapor deposited Mg-Ti-Y alloy, and (b) dead cells (curled up) on commercial WE 43. Cells were grown in culture media for 24 hr.

Cell culture experiments (A549 cells) showed the vapor deposited Mg-Y-Ti alloy to be more biocompatible than the wrought alloys (WE 43 and EV31). Figure 3 shows the results of exposures of the commercial WE 43 (EV31 results looked the same) alloys and the vapor deposited Mg-Y-Ti alloy to A549 cells. Healthy growing cells (spread out cells) attached to the vapor deposited Mg-Y-Ti alloy after 12 hours (Fig. 3a) and only dead cells (curled up cells) were noted for the ones exposed to the commercial alloy WE 43 (Fig. 3b). The death of cells on WE 43 may have been due to the higher corrosion rates of the commercial alloys.

It should be kept in mind that despite the fact that WE 43 did not pass the initial cell exposure tests, WE 43 stents have already been implanted in 63 cardiac patients in Europe in 2005 without deaths related to the implanted magnesium stents.

### Concluding Remarks

The future use of dissolvable magnesium-based alloys in the human body appears quite promising. Implants constructed from these materials have the potential to address a number of drawbacks associated with traditional implants like restenosis, thrombosis, and permanent physical irritation. Research on this very interesting topic is underway in Europe and in the U.S. For a successful application in the human body, detailed knowledge on the corrosion behavior of metallic

biomaterials is crucial—this holds both for implants where corrosion is desired (biodegradation) and for permanent implants where high-corrosion resistant alloys are used. The human body is a complicated environment and significant differences in Mg alloys dissolution rates are noted between in vivo and in vitro studies. The reasons for these differences need to be better understood and perhaps exploited in the development of new dissolvable Mg-based alloys. ■

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