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Review

The history of biodegradable magnesium implants: A review ☆

Frank Witte *

Laboratory for Biomechanics and Biomaterials, Department of Orthopaedic Surgery, Hannover Medical School, Anna-von-Borries-Str. 1-7, 30625 Hannover, Germany

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ABSTRACT

Today, more than 200 years after the first production of metallic magnesium by Sir Humphry Davy in 1808, biodegradable magnesium-based metal implants are currently breaking the paradigm in biomaterial science to develop only highly corrosion resistant metals. This groundbreaking approach to temporary metallic implants is one of the latest developments in biomaterials science that is being rediscovered. It is a challenging topic, and several secrets still remain that might revolutionize various biomedical implants currently in clinical use. Magnesium alloys were investigated as implant materials long ago. A very early clinical report was given in 1878 by the physician Edward C. Huse. He used magnesium wires as ligature for bleeding vessels. Magnesium alloys for clinical use were explored during the last two centuries mainly by surgeons with various clinical backgrounds, such as cardiovascular, musculoskeletal and general surgery. Nearly all patients benefited from the treatment with magnesium implants. Although most patients experienced subcutaneous gas cavities caused by rapid implant corrosion, most patients had no pain and almost no infections were observed during the postoperative follow-up. This review critically summarizes the in vitro and in vivo knowledge and experience that has been reported on the use of magnesium and its alloys to advance the field of biodegradable metals.

1. Introduction

The history of biodegradable magnesium implants started shortly after the discovery of elemental magnesium by Sir Humphrey Davy in 1808 [1]. His assistant, Michael Faraday, enabled the production of Mg metal by electrolysis of fused anhydrous $MgCl_2$ in 1833 [1]. The commercial production of Mg by electrolysis was realized by Robert Bunsen, who created a small laboratory cell for the electrolysis of fused $MgCl_2$ in 1852 [1]. At that time, Mg was produced in small quantities in America and Europe for pyrotechnical use, and as igniting bands or wires for flash lights of the upcoming photographic industry [1]. These initial Mg products were presented at the world exhibition in London in 1862 [1]. It is most likely that the physician Edward C. Huse used some of those Mg wires as ligatures to stop bleeding vessels of three human patients in 1878 [2]. He already observed that the corrosion of Mg was slower in vivo and that the time period until complete degradation was dependent on the size of the Mg wire used [2]. Huse wrote very enthausiastically about the degradable properties of the metal [2].

The most influential pioneer was the physician Erwin Payr from Graz, Austria whose versatile clinical applications and reports inspired many other clinicians to advance the field of biodegradable magnesium implants to various surgical areas (Fig. 1). He started his first experiments on Mg resorption in 1892 [3], but his main problem at that time was to get filigree fabricated devices made of Mg for his studies [3,4]. In 1898, Payr was supplied with pure Mg sheets and plates, pins, spheres, wires, pegs, cramps and nails from the company I. Rohrbeck in Vienna, Austria [3,4]. Around 1900, Payr already proposed that tissue oxygen and water content, carbon dioxide, the dissolved salts in blood and the chemical processes in cells were mainly responsible for the corrosion of Mg in vivo [3,4]. Albin Lambotte was also an early clinical investigator of biodegradable Mg and the mentor of his assistant Jean Verbrugge, who continued and extended the animal experiments and clinical studies [5–9]. An overview of authors who reported on the results on Mg for biomedical applications is given in Table 1. Since the problem of controlling the corrosion of Mg in vivo had not been sufficiently solved, many surgeons preferred to use the more corrosion-resistant V2A steel. Thus, Mg was no longer investigated intensively as a biomaterial [10]. These fascinating historic reports on various biomedical applications of metallic Mg in humans and animals are summarized in this review and structured

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* Tel.: +49 511 532 8961; fax: +49 511 532 8797.
E-mail addresses: witte.frank@mh-hannover.de, f.witte@web.de.

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Fig. 1. A portrait of Prof. Dr. Erwin Payr, the Austrian surgeon and pioneer in the field of biodegradable magnesium implants [37]. With kind permission from Springer Science + Business Media.

according to their clinical applications, along with the general findings of the in vitro and in vivo behaviour of Mg-based implants.[1]

2. History of magnesium production and possible origin of used magnesium

Sir Humphrey Davy, a British chemist, first isolated aluminium in 1807 and identified magnesium in 1808 [1]. Davy discovered many metals and their production processes [1]. Davy's assistant was Michael Faraday, who produced Mg metal by electrolysis of fused anhydrous $MgCl_2$ in 1833 [1]. Commercial production of Mg by electrolysis is credited to Robert Bunsen, the German scientist, who created a small laboratory cell for the electrolysis of fused $MgCl_2$ in 1852 [1]. The first Mg samples to be produced on an industrial scale were used mainly for pyrotechnical applications, and were presented at the world exhibition in London in 1862 [1]. At that time, small production lines of Mg for use in pyrotechnical and photographical applications were working in France, England and USA [1]. The commercial electrolytic magnesium production began in Germany in 1886, by using a modification of Bunsen's cell [1]. The Aluminium und Magnesium Farbik in Hemelingen (Germany) designed and built a plant for the dehydration and electrolysis of molten carnallite [1]. In 1896, this process was further developed by Chemische Fabrik Griesheim-Elektron, who transferred the process to its Bitterfeld works and became the main Mg producer in the world until 1916. Later Griesheim-Elektron became part of I.G. Farbenindustrie AG. Many magnesium alloys under the brand name Elektron were developed for technical applications, but were also used for biomedical applications (Table 1). Several smaller companies in the USA started the production of Mg before 1915, but only the American Magnesium Corporate and the Dow Chemical Company survived until 1925, and only the latter thereafter [1]. Smaller Mg productions were active from 1915 the 1940 in Italy and France [1]. In England, Mg production started in a small company in Wolverhampton around 1919, and at the beginning of 1937 the company Magnesium Elektron Ltd. started its still ongoing Mg production [1]. The purity of Mg and its alloys was mainly determined by the Mg source and the production process. Thus, the surgeons were mainly dependent on the available local Mg alloys or capabilities of the closest Mg supplier.

[1] All parameters and units are reported as given in the original literature.

3. Magnesium in cardiovascular applications

3.1. Wires and other designs for ligature

In 1878, Huse used a Mg wire ligature successfully to stop bleeding vessels three times: once in a radial artery and twice in the operation for varicocele [2]. Huse suggested using Mg wires also for ovariotomy and haemorrhoids [2]. In 1900, Payr regretted that the available Mg wires were too brittle to be a suitable suture material [3]. Therefore, Payr investigated tubular, thin-walled Mg cylinders as connectors for vessel anastomosis [3,4]. In 1924, Seelig was inspired by the work of Payr, Chlumský, Lespinasse and Andrews when he was considering Mg for ligatures [11] – even though Andrews had stated that pure Mg wires cannot be tied in even loose knots, as it breaks immediately on kinking, and it cannot be twisted due to its brittle nature [12]. As had previously been reported by Payr [3], Seelig had found in 1924 that the available Mg wires on the market were too brittle [11]. However, Seelig was encouraged to continue his research by a technical report from the Bureau of Mines of the Department of the Interior [11]. The bureau suggested using pure Mg that had been produced by distillation in vacuum to obtain more ductile Mg wires (for mechanical properties see Table 2) [11]. Furthermore, it was suggested that noble metals be alloyed with Mg to increase its ductility (e.g. gold or silver) [11]. The report also emphasized that marked ductility can be expected only in alloys which are solid solutions of one component in another [11]. Seelig was working in close cooperation with the American Magnesium Cooperation (Niagara Falls, New York). This company supplied chemically pure Mg (99.99%), which was extruded and drawn into wire ranging from 0.005 inch upward. Seelig started his experiments as soon as he had pure Mg wires in his hand, but these first wires had a low tensile strength and were not sufficiently pliable. Retrospectively, Seelig's ambitious action was somehow premature, and led to inappropriate results and conclusions.

In 1935, Gotthard Gossrau, from I.G. Farbenindustrie AG, patented an Mg rope which consisted of a mesh of thin wires (less than 0.1 mm) around an inner stronger guiding wire or intertwisted wire bundle [13]. While the inner guiding wire bundle guaranteed the tensile strength of the rope, the outer wire mesh guaranteed the consistency of the inner bundle. The outer wire mesh provided an additional advantage of a better grip of the surgical suture material. By this invention, the usually observed low tensile strength and knot stiffness of Mg wires was overcome. The low tensile strength and known stiffness were usually obtained during cold work hardening in the production process.

The inventor Richard Jorgensen filed a patent on a modified haemostatic clip design in 1986 [14], inspired by the absorbable metal clips that E.W. Andrews had published in 1917 as a substitute for ligatures and deep sutures [12]. Andrews found that the use of absorbable Mg clips and staples speeds-up and ensures the safety of haemostasis. He recommended that the clips and staples be used for closing vessels, e.g. in the brain, or for closure of deep wounds, intestinal anastomosis and other applications [12]. Andrews liked the fact that the absorbable metals were not acting as permanent foreign bodies. Even though he found most of the investigated alloys and pure metals as unsuitable, Andrews still persued making alloys that were ideal for various implant applications [12]. He tried to improve the ductility, flexibility and tough-

Table 1
Historical overview of reports on magnesium and its biomedical application in historical order.

Author	Year	Magnesium (alloy)	Supplier	Application	Human/ animal model	Ref.
Huse	1878	Pure magnesium	Not reported	Wires as ligature	Humans	[2]
Payr	1892–1905	High-purity Mg	I. and C.W. Rohrbeck, Vienna, Austria, Al und Mg Fabrik Hemelingen, Germany	Tubes (intestine, vessel, nerve connector), plates, arrows, wire, sheets, rods	Humans, guinea pigs, rabbits, pigs, dogs	[3,4,20,31–34]
Höpfner	1903	Pure magnesium	Not reported	Magnesium cylinders as vessel connectors	Dogs	[16]
Chlumský	1900–1905	High-purity Mg	Friedrich Wosch Company, Germany	Tubes, sheets and cylinder intestine connector, arthoplastik	Humans, rabbits, dogs	[21,39]
Lambotte	1906–1932	Pure Mg (99.7%)	Not reported	Rods, plates, screws	Humans, rabbits, dogs	[5,6]
Lespinasse	1910	Metallic magnesium	Not reported	Ring-plates for anastomsis	Dogs	[17]
Groves	1913		Not reported	Intramedullar pegs in bone	Rabbits	[23]
Andrews	1917	Pure Mg, mix. of eq. part: Mg/Al, Mg/Cd, Mg/Zn	Not reported	Wires, clips as ligature, anastomosis	Dogs	[12]
Seelig	1924	Pure Mg (99.99%), distilled in vacuum	American Mg Cooperation, Niagra Falls, New York	Wires, strips, bands	Rabbits	[11]
Glass	1925	Pure Mg (99.8–99.9%)	Al und Mg Fabrik, Hemelingen, Germany	Magnesium arrows	Humans, rats, cats	[36]
Heinzhoff	1928	Pure magnesium	Not reported	Magnesium arrows	Rabbits	[38]
Verbrugge	1933–1937	Dow Metal: Mg–Al6–Zn3–Mn0.2%-wt. Elektron Mg–Al8%-wt.	Dow Chemical Corp., USA Griesheim-Elektron, Germany	Plate, band, screws, pegs	Humans, dogs, rats, rabbits	[7–9]
McBride	1938	Mg–Mn3%-wt., Mg–Al4–Mn0.3%-wt.	Not reported	Sheet, plate, band, screw, peg, wire	Humans, dogs	[24,26]
Nogara	1939	Elektron (alloy not specified)	Griesheim-Elektron, Germany	Rods	Rabbits	[42]
Троицкий	1948	Mg–Cd	Not reported	Plate, screws, rod-plate	Humans	[28]
Maier	1940	Magnesium	I.G. Farben Industry AG, Bitterfeld, Germany	Band, suture from woven Mg wires, fusiform pins	Humans, rabbits	[27]
Stone	1951	Mg–Al2%-wt. pure magnesium	Aluminium Company of America, OH, USA	Wires for clotting aneurysms	Dogs	[19]
Fontenier	1975	Ind.-grade purity: Domal Mg (99.9%), T.L.H. Mg not reported Lab-grade purity: "zone fondue" Mg, R69 Mg MgMn1.5%-wt., MgAl:GAZ8%, GAZ6%, GAZ3%	Not reported	Anodes for implantable batteries to feed pacemaker	Dogs	[40]
Wexler	1980	Mg–Al2%-wt.	McMaster Univ. Med., Canada	Wires intravascular	Rats	[41]
Hussl	1981	Pure Mg (99.8%)	Goodfellow Metals Ltd., GB	Wires for hemangioma treatment	Rats, rabbits	[44]
Wilflingseder	1981	Pure Mg (99.8%)	Goodfellow Metals Ltd., GB	Wires for hemangioma treatment	Humans	[37]

Table 2
Variations in tensile strength and elongation of high-purity magnesium wires [11].

Diameter of wire (inches)	Tensile strength inch^{-2} (pounds)	Elongation in 24 inches (percentage)
0.020	35,170	4.0
0.015	39,044	2.8
0.010	43,513	1.73
0.009	43,333	1.37
0.007	45,610	1.20

ness of the magnesium alloys by preventing oxidation during the mixing. He produced Mg alloys consisting of equal parts of Mg and Al, Mg and Cd, and Mg and Zn, as well as one mixture of 25% Mg, 35% Zn and 40% Al. However, he discovered that all these alloys were too hard and brittle, and without sufficient tensile strength for cardiovascular application [12].

3.2. Connectors for vessel anastomosis

In 1900, Payr used pigs and the femoral artery of dogs for his experiments on vessel connectors made of Mg [3,4,15]. Payr was able to use tubal Mg connectors for the anastomosis of arterial and venous blood vessels; in the later case, the inner part was placed into the peripheral end of the vessel to take into account the venous blood flow direction (Fig. 2) [4]. Payr found that the connection of the vessel ends became solid after 8 days, and observed a severely thickened intima layer at the anastomosis, with a fibrous ring on the outer side at that point [3,4]. Payr observed that the thickness of the vessel returned to normal after he has been waiting more than 8 days before he reinvestigated the anastomosis [4]. Payr stated that only the intravascularly placed Mg tubes exhibited thrombotic blood clotting at the end of the tubes, which, however, never closed the remaining lumen; no thrombosis was observed with extravascularly placed Mg tubes [4]. Höpfner [16] also rarely found thrombosis in the area of his extravasal pure Mg cylinders which were modified based on the cylinder design of Payr. Höpfner observed thrombosis only in vessels with a diameter less than 3 mm due to extensive intima lesions during the operation, while no thrombosis occurred in larger vessels in 25 anastomoses in dogs after 4 weeks.

In 1910, Lespinasse introduced a technique for extravasal sutures of vessels using metallic ring plates with punched holes to fix the vessel ends and connect the rings with a pressure of less than 5 lbs [17]. The period within which the extravasal Mg rings were completely absorbed varied from 80 to 100 days. The Mg ring plates were found to maintain their original shape for about 30 days before they began to break down. Lespinasse also introduced a Mg plate with holes suitable for the repair of a lateral slit

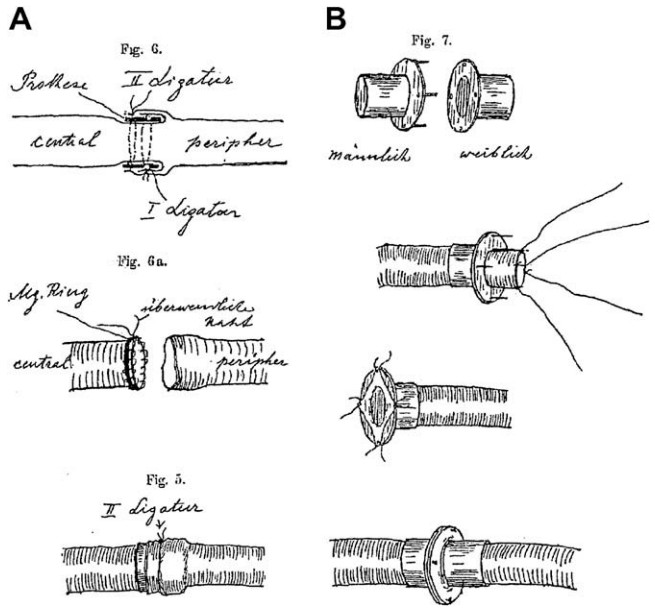

Fig. 2. Tubal magnesium connectors designed by Payr for vessel anastomosis [3]. Method (A) used an extravasal magnesium ring, which ensures an open postoperative anastomosis. Method (B) uses a two-part extravasal connector with a male and female part. In both methods the magnesium connector is extravasal and the anastomosis is achieved by a duplication of the intima. Thus, no foreign material is located intravasal after the anastomosis.

in a vessel [17]. The use of Mg ring plates prevented foreign material in the lumen of the reconnected vessels, and hence the vessels were free from clots. This finding was also observed by Payr [3]. The Mg rings were tied firmly together, but not so tight as to cut the intima and cause vessel necrosis [17]. Thus, Lespinasse [17] observed no secondary thrombosis or secondary vessel constriction in his experiments, which were both reported by Payr [3]. The application of Mg as a biodegradable metal stent is a more recent development, which started around 1998 by the group of Heublein et al. A more detailed review of biodegradable metal stents can be found elsewhere in this issue [18].

3.3. Wires for aneurysm treatment

In 1951, Stone and Lord looked for a thrombogenic material to favour intrasaccular clotting in aortic aneurysms [19]. They used pure Mg wires (0.025 inch diameter) and Mg–Al wires (0.03 inch diameter) in dogs' aortas as double-coiled wires and found that Mg wires were twice as thrombogenic as stainless steel and that the thrombogenic potential of Al-alloyed Mg wires was as much as three times higher than that of stainless steel [19]. The pure Mg wire was very brittle, while the addition of 2% Al allowed bending and clinical application. Stone and Lord stated that both wires were suitable for the intended application, while the Mg–2% Al exhibited a higher thrombogenic potential than commercially pure Mg [19]. However, Seelig observed that the thrombus formation was only present at Mg wires regardless of their composition [11]. Seelig found that the pure Mg wire and Mg–2% Al wire attached to the intima after 21 days of implantation [11]. The pure Mg wires were intact and enveloped with a grayish pseudomembrane consisting of finger-like processes of collagenous tissue which connected the wire firmly with the intima [11]. At these sites the internal elastic membrane and intima were absent. In contrast, the Mg–2% Al wires had undergone almost complete dissolution after 21 days. The Mg–2% Al wires were only identifiable as metallic particles enmeshed in the thrombus. The lack of radiopacity of commercially pure Mg and alloyed Mg–2% Al wires was given as a limitation for several clinical applications. Stone and Lord recommended using Mg in saccular aneurysms instead of fusiform aneurysms of the aorta, since the latter bear the risk of rapid thrombus formation and possible embolization [19].

4. Magnesium in musculoskeletal applications

4.1. Resectional and resurfacing arthoplasty to regain joint function

In 1900, Payr introduced the idea of using Mg plates and sheets in joint arthoplastics to regain or preserve joint motion, but after frustrating animal experiments and clinical observations he waived this treatment option [3,15]. At the 29th Congress of the German Society for Surgery in 1900, Chlumský listened to Payr advising that Mg sheets and plates be used to prevent the reunion of dissected bone tissues by a dense fibrous layer after full resorption of the Mg metal [4,20]. This talk of Payr inspired Chlumský to investigate Mg to regain motion in stiff joints, e.g. knee ankylosis caused by tuberculosis or the stiff jar joint [3,21]. In his experimental work, Chlumský interposed 0.1–0.8 mm thick Mg sheets between the freshly separated bone surfaces in the knee joints of dogs and rabbits [10,21]. The Mg sheets were completely corroded after 18 days or a few weeks, depending on their thickness [10,21]. Chlumský was successful in preventing joint stiffness, and he restored joint motion after bony separation of ankylotic joints in animals and humans [21]. In a human case, Chlumský demonstrated the preservation of a 2 mm wide joint space on X-rays at 8 months after operation [15,21]. Chlumský usually temporarily stabilized the newly formed joints by an external plaster fixation [21]. Therefore, he was concerned that these neo-joints would become stiff again over the years [10,21].

4.2. Osteosynthetic applications

In 1900, Payr proposed possible Mg implants in musculoskeletal applications, including fixator pins, nails, wires (cerclage), pegs, cramps, Mg sheets and plates [3,10,20]. Furthermore, Payr described a Mg peg as an intramedullary stabilizer for irreponable bone fractures and pseudarthrosis [4,20]. In 1906, Lambotte first investigated Mg implants in a 17 year old child who had suffered from a complicated pseudarthrosis with severe malalignment of the distal third of the lower leg based on a 2 month old fracture of the lower leg [5,6]. Lambotte initially used an iron plate with an iron screw fixation, which resulted in a clinical failure [6]. After 4 months, the fracture ends were only loosely attached by a fracture callus, and hence Lambotte had to retrieved the iron osteosynthesis material [6]. After a lag time of 1.5 months, Lambotte resected the fracture ends again and used an external fixature treatment for temporary fracture stabilization. Five months later, Lambotte decided to finally stabilize the fracture by using an iron wire cerclage at the fibula and a Mg plate with six steel screws at the tibia. One day after the last operation, the boy experienced extensive subcutaneous gas cavities, local swelling and pain. Due to the heavy pain, Lambotte removed the Mg plate in small fragments 8 days later. Finally, 8 months later, Lambotte treated the fracture with a bone transfer from the upper third of the unilateral tibia.

Lambotte was shocked by this clinical case, and had learnt that Mg dissolved due to the electrochemical reaction between the Mg plate and the steel screws. He decided to investigate this phenomenon together with his assistant Verbrugge in animal experiments. They found total resorption of magnesium between 7 and 10 months in rabbits and dogs [6]. Total absorption of Mg and no postoperative pain encouraged Lambotte to continue his clinical

investigations. He decided to treat supracondylar fractures of children, because these fractures heal quickly. Furthermore, he could insert a Mg nail with a small implant volume extra-articularly (Fig. 3). In total, Lambotte and Verbrugge operated on 4 children (7–10 year old) with supracondylar humerus fractures, which all healed per primam without complications (except the gas cavities), with good to total restoration of the joint function and with no pain in the operated area [6,8]. The evolved gas cavities disappeared after several weeks and were not a major concern in any clinical case [6]. Lambotte learned from his previous clinical experience. He waited for more than a year after operating on the first 7 year old child to observe the clinical outcome before operating on the next children (Fig. 4). In these cases, Lambotte observed the total resorption of Mg at 1 year after the surgery and physiological bone healing (according to X-rays) without any hypertrophic bone [6]. These clinical results encouraged Lambotte to extend his clinical investigation by operate on a child (8 year) with a transdiaphyseal humerus fracture [6,8]. Verbrugge reported later that this child had been treated with a Mg plate and screw fixation (Fig. 4A) [8]. Three weeks after the operation the metal plate had almost completely

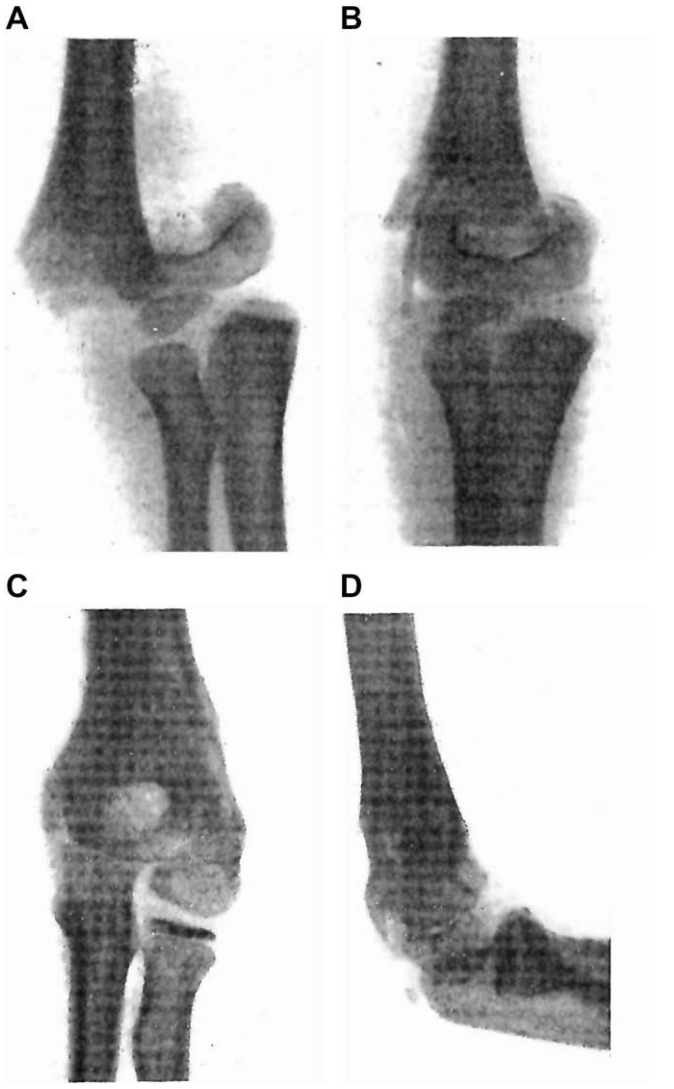

Fig. 3. Lambotte shows a supracondylar humerus fracture of a child (A), which was fixated using a magnesium nail (B). After several months the magnesium nail was totally corroded and the fracture was stable as presented in the two plane X-rays (C and D). No infection or pain occurred. The child had a good clinical function of the elbow [6].

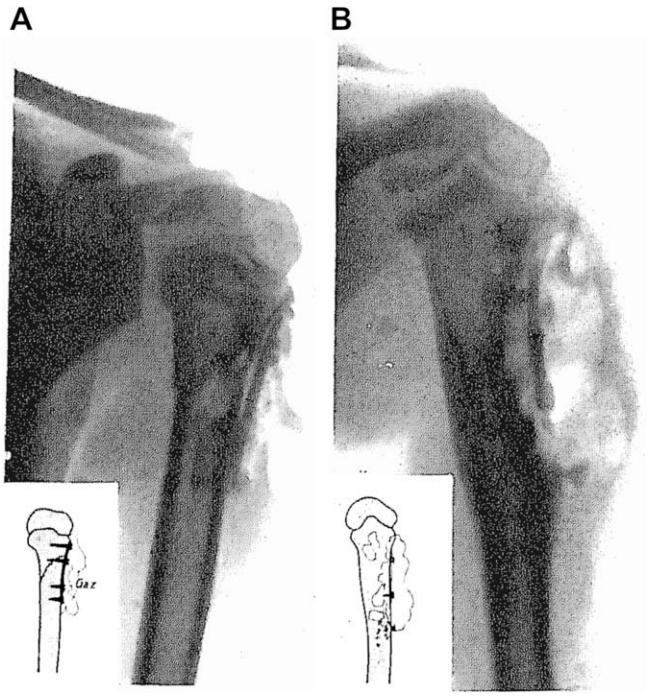

Fig. 4. Verbrugge used a magnesium plate and screws to stabilize a diaphyseal humerus fracture in an 8 year old child. (A) Postoperative X-rays demonstrating already formed gas cavities; (B) the magnesium plate was mainly corroded at 3 weeks after the operation [9].

dissolved and the bone fracture line was no longer visible (Fig. 4B) [8].

Lambotte learned that Mg could only be implanted without combining it with other metallic implants to prevent electrolytic corrosion [6]. Based on his good clinical results, Lambotte recommended the use of Mg implants in the following clinical areas: Bennet fracture, scafoid fractures, foot surgery, clavicular fractures, carpus fractures, phalanx and metacarpal fractures, radius epiphyseal fractures, lower arm diaphyseal fractures, supra- and condylar fractures in children (Fig. 5), humerus head fractures, malleolus fractures, oblique tibial fractures and pertrochantic fractures [6].

Also, Henschen and Gerlach stated in their review in 1934 that resorbable Mg plates and screws seemed to be the ideal osteosynthesis material [22]. However, there have been also critical reports on the use of Mg in bone applications, which were mainly based on animal experiments. Groves published his experiments on rabbits in 1913, when he condemned the use of Mg, because it seemed to produce abscess cavities and disintegrated so quickly that it was undesirable for stabilizing the fragments in the fracture [23]. He investigated the Mg metal as an intramedullary peg [23,24]. In 1924, Zierold compared the reaction of various metals on bone tissues and concluded that Mg has little action other than as a connective tissue stimulant, and hypothesized that it may retard as well as accelerate new bone production [2,4,25]. Verbrugge knew the critical statements and results of Zierold and Groves on Mg in bone application. However, as an assistant of Lambotte, Verbrugge investigated a 2.5 mm thick solid Mg cylinder in the femura of rabbits and dogs [7]. The Mg cylinders corroded slowly over 4 months under moderate gas evolution. Verbrugge described that the Mg cylinders still resisted the pressure of fingertips after 4 months [7]. After 6 months, he observed that the Mg cylinders became hollow and brittle. The surrounding tissue showed no signs of tissue irritation or inflammation [7,14]. After 3 weeks, no reaction had been observed, while after 7 weeks stronger reactions were found which faded after some months. Verbrugge stated that

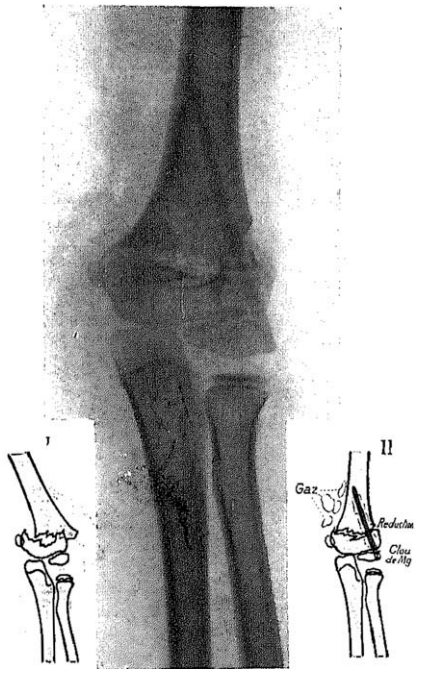

Fig. 5. Verbrugge demonstrated a postoperative X-ray of a supracondylar fracture of a 7 year old child treated with a Dow magnesium nail [9]. The early onset of subcutaneous gas formation can be seen [9].

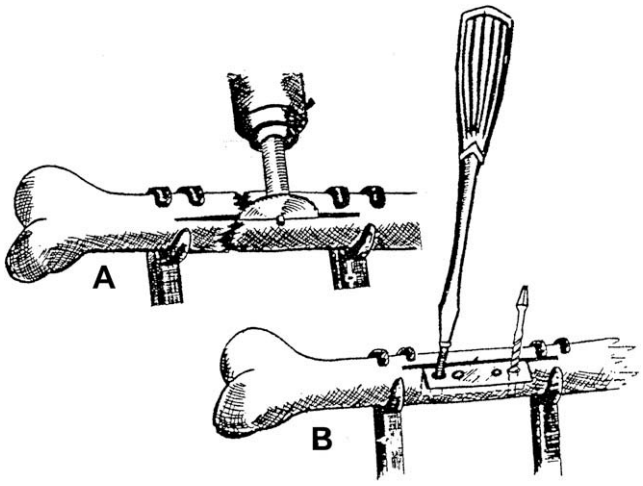

Fig. 6. McBride demonstrates a method of applying Mg–Mn as a thin angled plate and screws to achieve rotation-resistant osteosynthesis [26].

the concomitant gas evolution was not harming any tissue [7]. For his clinical investigations, Verbrugge used an Elektron metal (Mg alloy, composition not reported) and the Dow metal Mg–8 wt.% Al in 21 clinical cases [8]. Verbrugge observed hydrogen cavity formation without any adverse clinical effect during the postoperative phase 8 (Fig. 5). The patients reported a temporary "sleepy" feeling in the area of the implant during the period of Mg degradation, but the sense of touch and temperature was not disturbed [9]. All patients experienced regular body temperatures and no other signs of infection [8,9]. The skin, soft tissue, bone and joints showed no adverse reactions to the corroding magnesium [8,9]. The periosteal reaction was as strong as with usual non-absorbable implants or conservative treatments [8,9]. Verbrugge stated the implanted Mg is not toxic nor an irritant, and also reported that slow corrosion of the Mg is necessary to allow sufficient callus formation [8,9].

Around 1938, McBride was attracted by the work of Jean Verbrugge in Antwerp and followed his work after a personal communication [24,26]. Afterwards McBride received some initial Mg material from Verbrugge [24,26]. McBride found that plates made of Mg metal were not suitable because of the more rapid adsorption that seemed to occur when the plates were placed on the bone surface [24,26]. He also stated that Mg metal is not suitable for medullar pegs because its volatile gas-forming reaction requires an exit into the soft tissue [24]. McBride observed that screws were more resistant to corrosion than plates, especially when the screws were fitted more tightly into hard cortical bone [24]. The screws should penetrate both sides of the bone shaft and should have a higher quantity of Mg than needed for the expected time period for better and saver fixation [24]. McBride used a drill and threader tap corresponding to the size of the screw [24]. He also described several operation techniques which were adapted to the use of Mg implants (Fig. 6) [24,26]. Furthermore, McBridge suggested a three-corner design for Mg bone pegs [24]. He also stated that the Mg alloy is not toxic but creates a localized disturbance of the tissue, which however, limits its use to those cases where absorption is of distinct advantage and where stress of the fragments will be very slight after 3–5 weeks [24]. McBride supported Lambotte's and Verbrugge's view that Mg implants should not be used with other metals because of the risk of forced electrolytic corrosion. The Mg alloys employed by McBride remained stable from 3–7 weeks and accomplished firm fixation if the drill holes were not too large to permit retention of the threads and if the screws or nails were applied to a good mechanical advantage of the leveraged bone fragments, especially in oblique or condylar fractures. The Mg metal stimulated the early proliferation of connective tissue and caused an overproduction of callus, which should not be trusted too early for firmness. McBride further recommended that Mg implants be used in compound fractures and in the fixation of autologous grafts, where the ready-threaded screws could save operation time and produce a firm fixation.

In 1940, Maier investigated pins made of spindle-shaped Mg sheets in two humerus fractures in humans [27]. In one case the healing process was uneventful, while in the other case the implant was removed only 12 days after the operation due to the continuous formation of gas cavities. In both cases, Maier observed a good functional result after 14 years. These spindle-shaped pins have been reported to be very resistant against bending and shear [27]. Based on his good clinical results, Maier started experiments in rabbits [27]. he implanted a band of Mg subperiostally into the rabbit tibia and observed the Mg corrosion and the formation of gas cavities, as well as extensive periostal bone formation, which he related to the strong irritant effect of the corrosion product magnesium oxide [27]. He suggested using Mg for arthrodesis of joints and in spinal surgery.

In 1948, Troitskii (Троицкий) and Tsitrin (Цитрин) reported the successful treatments of 34 cases of pseudarthrosis with a plate and screw combination made of an Mg–Cd alloy [28]. The osteosynthesis material was resorbed completely, without any remaining, and stimulated the formation of callus bone [28]. This bone-stimulating effect was hypothesized to be based on the formation of $MgCO_3$ observed in the corrosion layer [28]. Troitskii, Tsitrin and Verbrugge stated that the implantation of Mg into inflammatory tissue causes neutralization of the acid environment and would thus stimulate the formation of callus bone [8,9,28]. Thus, Troitskii and Tsitrin suggested the use of a specially designed intramedullary rod/plate implant made of a Cd-containing Mg alloy to obtain an exact bone reposition and the rapid consolidation of the fracture in severe cases of osteomyelitis [28]. Based on their own clinical observations, this treatment led to the faster recovery of patients.

Interestingly, a patent for alloying Cd to Mg to improve the corrosion resistance was filed by Stroganov in 1969 [29], even though the equilibrium diagram of the Mg–Cd system had been already investigated by Hume-Rothery and Bowell in 1927 [30].

5. Magnesium in general surgery

5.1. Well-vascularized parenchymateous organs

Payr recommended using Mg sheets and plates for suturing well-vascularized parenchymatous organs such as liver and spleen in 1900 (Fig. 7) [3,4,31]. This was especially effective after partial liver excision, which Payr first tried successfully in animals and than also tried successfully in a human case [15,31]. Payr and Martina excised a cancerous gall bladder in a 54 year old woman with a significant part of the liver, closed the wound and bleeding tissue by using Mg plates to adjust the liver resection surfaces and connected the plates with iodine-catgut sutures [31]. Payr discovered in dog and rabbit experiments that the Mg plates were resorbed in the liver at various intervals, ranging from 3 weeks for 50% resorption of large Mg plates to minor resorption after 5 weeks [15,31]. Payr and Martina extensively described different liver and speen resection methods [31]. Extensive fibrous tissue formation in the resorbed Mg areas was impregnated with tiny bubbles of hydrogen gas [15,31], which stopped local bleeding by the tamponade effect [31]. This local tamponade effect was enhanced by adhesion of omentum majus, intestine and the abdominal wall to the resection area [31]. After 14 days of continuous Mg plate resorption, the fibrous tissue formation diminished [15,31].

5.2. Haemangioma and large-vessel aneurysms

In 1900, Payr also recommended using Mg to treat cavernous haemangioma and large-vessel aneurysms (Fig. 8) [3,4,32–34]. Payr treated an extensive haemangioma cavernosum at the chin of a 14 year old girl with Mg arrows (Fig. 8) [32]. Payr found that the tumor was getting denser within the first days after treatment, and the evolution of hydrogen could be observed as a small emphysema on day 1 after treatment. The implanted arrows were not detectable by palpation after 8 days. The soft swelling was reducing in size and was replaced by a denser, less voluminous nodule [15,32]. The insertion of Mg arrows in haemangiomas and lymphangioma tumors is based on the obliteration of the tumor by enhanced blood clotting from the mechanical destruction of the endothelium and the septa of the tumor, while the evolving hydrogen gas accelerates the local blood clotting directly [32,33]. These blood clots with embedded gas cysts were reorganized by fibrous tissue, obliterating the haemangioma [32,33]. Remarkably,

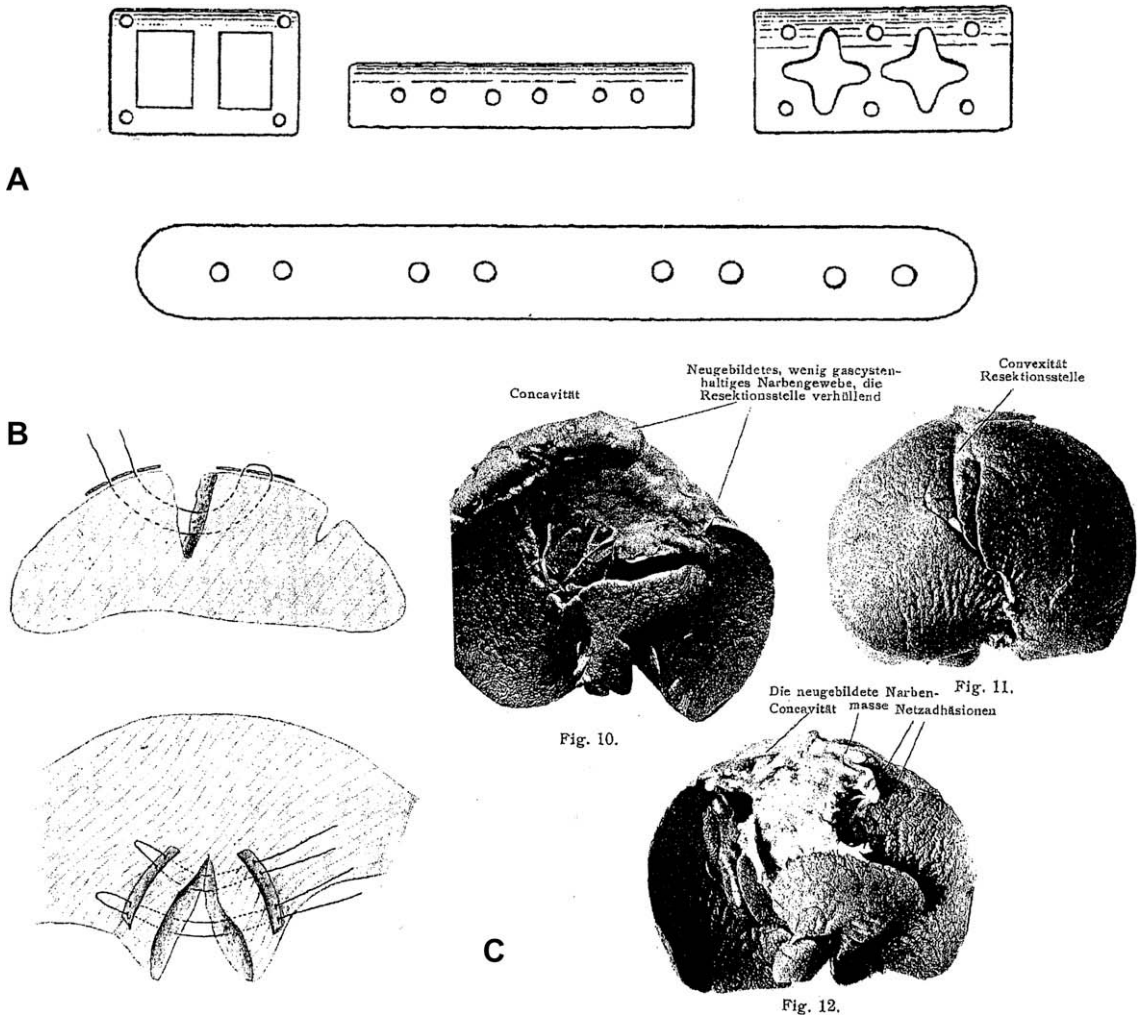

Fig. 7. During 1900–1905, Payr was investigating the use of various magnesium plates (A) for different suture techniques of parenchymatous organs (B), such as spleen and liver, in animal experiments and in one human case [31]. Payr could successfully demonstrate the use of magnesium plates in partial resections of rabbit (C) and dog livers [31].

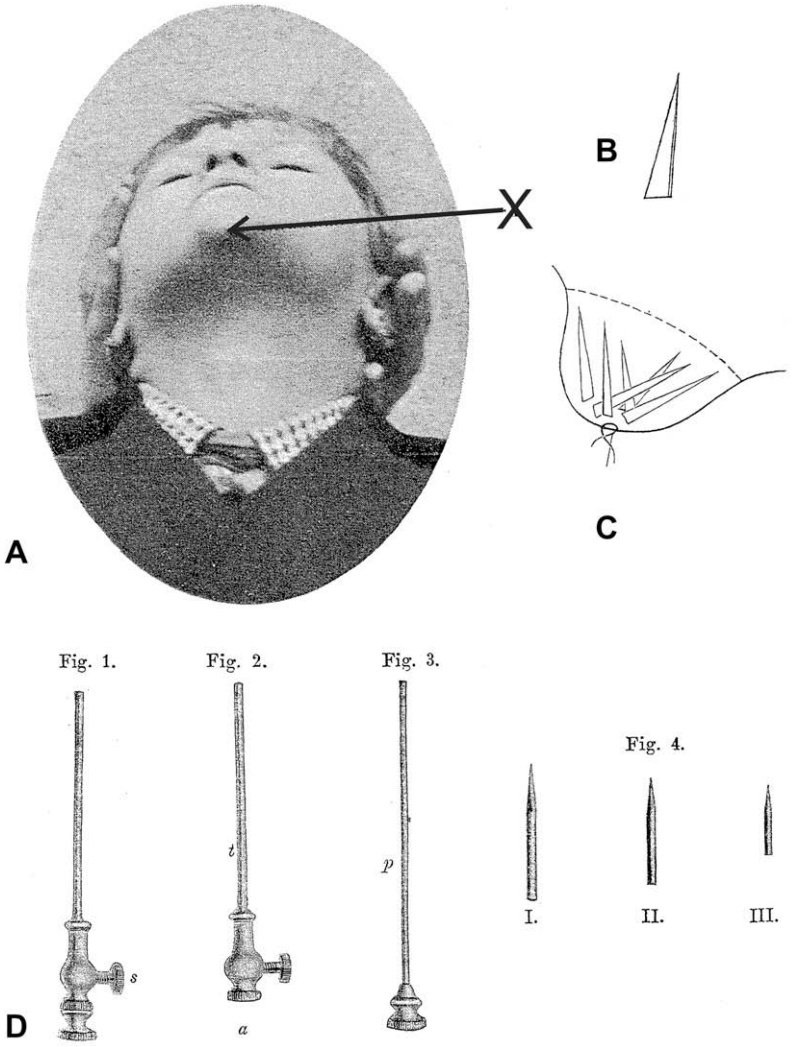

Fig. 8. For the minimal invasive treatment of cavernous haemangioma (A; × marks the insertion point), Payr recommended in 1900 the insertion of high-purity magnesium arrows (B) directly into the tumor (C) [32,33]. In a more detailed description of the method he used platinum–iridium trocars to insert the machined magnesium rods into the haemangioma (D) [33]. With kind permission from Springer Science + Business Media.

Payr never observed gas embolization in his patients [3,4,15,32–34]. After several years of clinical experience, Payr summarized that the Mg arrow treatment was only beneficial for treating subcutaneous cavernotic haemangioma [31,33]. This indication was confirmed by Sonntag [35], who also described the technique extensively in addition to Payr's original reports [32,33]. Payr even recommended the insertion of Mg arrows using local anaesthesia and a minimal invasive approach (Fig. 8) [32]. Glass could not repeat Payr's results of haemangioma treatment in two patients [36]. Glass performed additional animal experiments in cat kidneys and subcutaneously in rats, and stated that Mg arrow therapy may not be beneficial for large and not purely cavernotic haemangioma.

In 1981, the group of the plastic surgeon Wilflingseder repeated Payr's Mg arrow treatment in 27 haemangioma patients [37]. A good clinical result was obtained only in 50% of the cases, since various types of haemangioma were treated. No adverse effect was observed in a 5-year follow-up [37]. However, Wilflingseder et al. obtained remarkable results in a haemangioma of a 3 month old baby (Fig. 9).

Hoffheinz and Dimitroff implanted Mg into the spleen and ear vein of rabbits and found that faster corrosion with extensive gas evolution can be found in more blood-enriched organs, such as the spleen, or a haemangioma [38]. Hoffheinz and Dimitroff concluded from their experiments in rabbits that Mg corrodes quickly in haemangioma, which leads to the early transformation of the haemangioma into a fibrous granulation tissue.

5.3. Connectors for intestinal anastomosis

Chlumský presented his investigations in using Mg tubes as connectors of intestine anastomosis in his hometown Breslau at the 29th conference of the German Society for Surgery in 1900 [4,20,39]. He reported about sharp edges, ridges and splints on the Mg connectors, and professed that he was not convinced about the suitability of Mg [4,20]. However, Chlumský became inspired by Payr's work and his Mg supplier, and finally he was convinced that Mg could be used successfully as an implant material after switching to high-purity Mg, which corroded very homogenously in vivo [20,39]. Chlumský described in detail the design of the tubal Mg connector, which consisted of a male and a female part. The male part comprised a kind of Mg spring to secure the connection of both parts after joining [39]. He observed that Mg implants were significantly corroded after 8 days in a dog's stomach, but were still mechanically stable (Fig. 10). The corrosion rate was lower in the

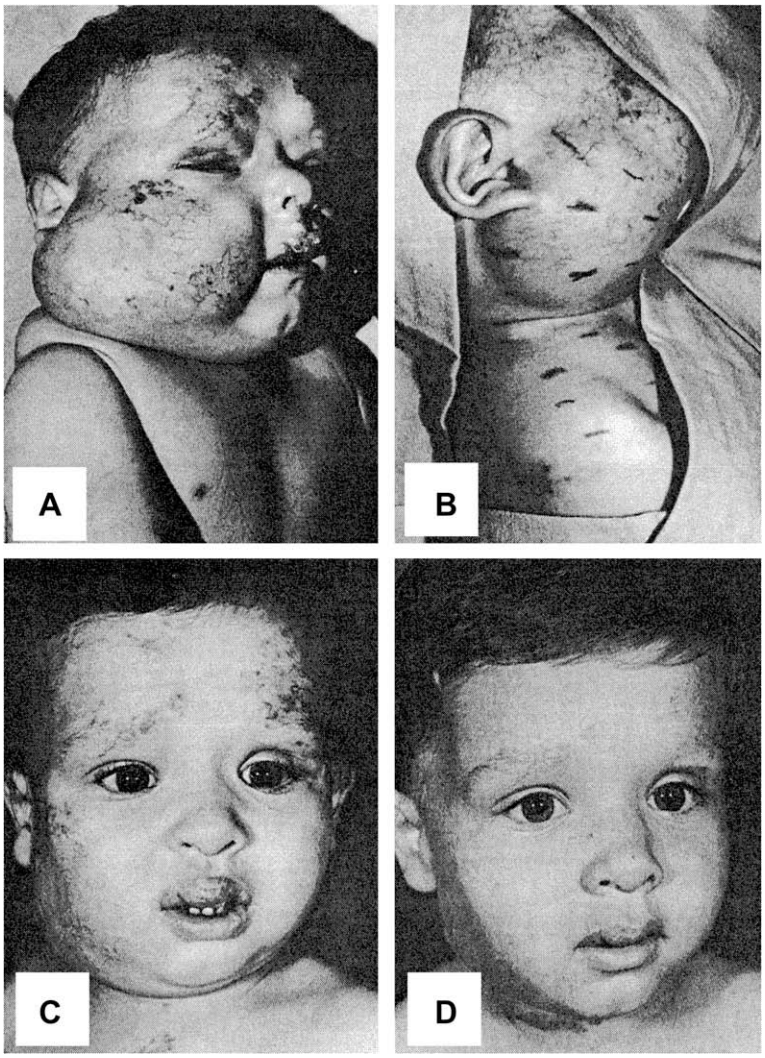

Fig. 9. Wilflingseder et al. repeated successfully Payrs treatment of cavernous haemangioma in children [37]. (A) A 3 month old child with proliferating haemangioma of the face, throat and shoulder. (B) The same patient as in (A); the incisions for the insertion of the magnesium arrows are marked with ink on the skin. (C) After 3 weeks the treatment was repeated and 9 months after the beginning of the treatment a significant reduction of the haemangioma could be observed. (D) After an additional insertion of magnesium arrows at 3 months, the face of the 2 year old child became almost normal at 20 months after starting the magnesium treatment. With kind permission from Springer Science + Business Media.

intestine and took 2–4 weeks for complete breakdown, depending on the anatomical location and the size of the implant. After the successful use of these connectors in humans, Chlumský also suggested controlling the preferred implant's breakdown in the intestine over 8–10 days by the oral administration of acid nutrients or diluted hydrochloric acid (4–5 drops per glass of water), thereby also preventing the occurrence of sharp edges and ridges on the implant or its degradation products [39].

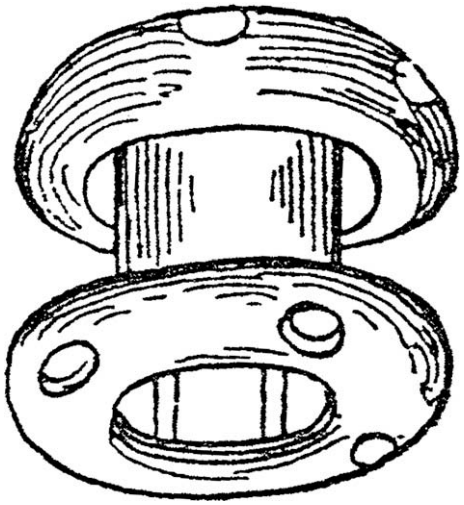

Fig. 10. In 1907, Chlumksý demonstrated an intestinal connector, consisting of a male and a female part, which uses a magnesium spring mechanism to seize both parts [39].

5.4. Design of magnesium suture material

Inspired by Payr's clinical success and the pressure from both German industry and the science administration at that time to replace the generally used catgut and Carnofil suture material with substances that could be produced in Germany, the MD–PhD student Siegfried Vordemann investigated Mg–Zr threads consisting of 31 single Mg wires which were implanted subcutaneously in the paravertebral region of rabbits [15]. The dimensions of the thread were given as $12 \times 3 \times 0.05$, thus it may perhaps have been a textile band rather than a round thread or rope. Vordemann observed the first subcutaneous emphysema, as a sign of early hydro-

gen gas evolution, 30 min after implantation [15]. The gas evolution increased until day 5, before decreasing again. The progressing corrosion of the Mg–Zr thread resulted in the loss of hardness and strength by 15 days, when it could be cut by scissors. After 50 days, the thread was almost completely corroded.

As a further application of Mg sutures, in 1900 Payr suggested the use of Mg wires for Bassini sutures [4]. Maier also used sutures made of woven Mg wires as Bassini sutures in hernia surgery, though he did not find them very convincing, since the gas evolved from the suture holes [27].

5.5. Connectors for neurorrhaphy

In 1900, Payr also suggested to use Mg tubes for primary and secondary sutures of nerves [3,4,15]. The Mg tubes are protecting the point of adaptation and reduce the number of catgut sutures to one inner nerve suture aligning both nerve ends and one or three very fine paraneutrotic nerve sutures [4]. Payr used this technique in several animal trials and also several times in humans (nervus medianus 2×, nervus peroneus 1×, nervus vagus 1×, nervus ulnaris 4×) [4].

5.6. Biobatteries for pacemakers

In 1975, Fontenier et al. investigated in vitro and in vivo the use of various Mg metals as dissolvable anodes for bioelectric batteries to feed pacemaker [40] (Table 1). He found that the industrial-grade-purity magnesium Domal (99.9%) was superior to the Mg–Mn alloy due to the possible toxicity of manganese, even though both alloys did not show any subcutaneous necrosis in dogs and corroded very uniformly [40].

6. Tissue response to corroding magnesium

6.1. Vessels and subcutaneous tissue

Several authors have reported on the severe influence of corroding Mg on the peri-implant tissue [3,4,10,20,31,33,32,34]. Payr and Vordemann observed similar histological results in the perivascular tissue of humans and the subcutaneous tissue of rabbits. A huge number of round cells and granulation tissue were observed around the corroding Mg [3,4,10,15]. The granulation tissue had a mucous consistence and contained foreign body giant cells with several little black metallic particles as foreign body inclusions [10,15]. These inclusions were also observed in leucocytes [10,15]. The granulation tissue was highly vascularized [3,4,15]. Payr reported macroscopic and microscopic pathological findings of healed intima layers in a human vessel 3 days after anastomosis by a Mg prosthesis [4]. The patient died due to pneumonia [4]. During the post-mortem examination, Payr could not observe any intima lesions from the Mg prosthesis, which had severely degraded within the 3 days after implantation [4,10].

Payr observed the strong activation of blood clotting from corroding Mg implants, which was enhanced even further with continuing hydrogen gas evolution [31]. Höpfner investigated an extravasal Mg cylinder for anastomosis of dogs vessels [16]. Höpfner found that the Mg cylinders were completely corroded and metal particles and gas cavities were found in the surrounding tissue. If no thrombosis happened, only a black surface of the Mg implant that was partly eroded could be observed [16]. The corrosion rate of the Mg cylinder was not constant, and after complete corrosion a scar was formed. Interestingly, Höpfner observed faster corrosion in limbs that were allowed to move freely.

In 1980, Wexler investigated the pathophysiological responses of spontaneously hypertensive rats to Mg–Al wire implants in abdominal aorta, carotid and renal arteries [41]. He found that the Mg–2% Al wires dissolved within 1–2 weeks and caused an increase in adrenal glandular weight, thymic involution, depression of the abnormally elevated blood pressure and a retarded gain in weight after surgery compared to the non-operated control group. He also found that the serum enzyme levels of CPK, SGOT, SGPT and LDH were elevated and that corticosterone and deoxycorticosterone secretion was increased, while circulating levels of triglycerides and cholesterils were reduced in the operated group [41]. Histologically, fibrocellular intima lesions were observed around the Mg–2% Al wire. Wexler also observed occlusive thromboses with cholesterol-positive clefts in Mg–Al-implanted carotid arteries of spontaneously hypertensive rats with pre-existing arterial diseases.

6.2. Bone tissue

Lambotte observed that periostal proliferation progresses from 3 weeks after implantation to a maximum after 7 weeks, then decreases back to normal level after some months [6]. Contrary to Lambotte's statement that Mg enhances bone regeneration [6], Zierold postulated the opposite [25]. Verbrugge performed transarticular joint fixation by screws in three rabbits and transdiaphyseal (bicortical) insertion of Dow metal pins in 10 rabbits [9]. In both cases, the bone marrow was replaced by fibrous granulation tissue and the formation of new bone without the appearance of osteoclasts, while the periost was highly vascularized and thickened. Verbrugge found cystic cavities in the newly formed bone tissue [9]. However, he never observed any change in the blood count of his animals.

McBride observed that corrosion was slower in intramedullar Mg pegs than in transcortical applications, and observed the concomitant marked stimulation of periosteal bone formation [24]. He did not observe any adverse reaction on articular cartilage. Furthermore, he found no inflammatory tissue reaction adjacent to the corroding metal, though he did find small gas cysts with separation of muscle bundles and a locally increased amount of extracellular fluid.

In 1939, Nogara was inspired by Verbrugge's work and investigated the effects of small corroding pieces of Elektron magnesium on rabbit bone tissue [42]. He found that it corrodes under the evolution of gas cavities without harming the surrounding bone tissue. However, the gas evolution led indirectly to slight bone damage, which appeared to be repaired after complete metal corrosion.

Nicole investigated the effect of metals and their corrosion products on various tissues in rabbits and dogs [43] and found that there is a reactive inflammation with the tendency to form a fibrous capsule around the corroding pure Mg samples. Furthermore, Nicole found a spongy tissue formed by several gas cysts and a local oedema. In particular, large-volume Mg implants showed incomplete resorption, with a remaining slurry substance and accompanying gas formation. Nicole reported a surprisingly low corrosion rate of pure Mg in bone and an almost complete corrosion at 2 months. Compared to other metals, the long-term storage of metallic corrosion products in bone could not be observed for magnesium.

6.3. Nerve and muscle tissue

In 1981, the research group of the plastic surgeon Dr. Wilflingseder in Insbruck, Austria revisited Payr's work on haemangioma treatment [3,7,44]. To investigate the safety of Mg implants, they implanted subcutaneously and intramuscularly pure Mg wires (99.8%) with a diameter of 0.25 and 0.50 mm in rats and rabbits [44]. They found that the Mg wires were totally absorbed within 20 weeks under extended hydrogen gas cavity formation, but the

wires corroded even faster if pretreated with 10% acetic acid before implantation. They found only very mild foreign body reactions around the corroding Mg wires, and the structure and function of the neighbouring nerves and muscle fibres were preserved as shown by electromyographic studies. From their results, they concluded that the use of Mg in haemangioma is safe even in the close proximity of facial nerve branches and delicate muscle fibres.

6.4. Infection

Around1900, Höpfner and Payr observed no infections, although they were operating under non-ideal and non sterile conditions [3,4,16]. Hoffheinz and Dimitroff observed no infections, abscess or peritonitis in more than 40 Mg implantations over a period of 12 weeks [38]. Lambotte stated that the metal will dissolve after 9–10 months without any infection or pain [6]. In contrast, Bufe et al. assumed that the cystic subcutaneous foam formed by the hydrogen production of injured light metal workers was reducing the local immunity of the tissue, leading to a higher risk of bacterial infection [45].

7. Corrosion of magnesium in vivo and corrosion products of magnesium

7.1. Corrosion morphology and corrosion rate

It was reported by Payr in 1900 that Mg implants exhibited rough surfaces as well as shallow pits and small cavities after 24 h, which united during the ongoing corrosion process to form channels and cracks until the metal totally dissolves [3,4,10]. Payr determined a degradation rate of 0.1 g of pure Mg per 3–4 weeks in humans [3,4], which varied widely with the thickness of the intravascular tubes used and the blood vessel density at the implantation site [3,4]. Payr stated that high-purity Mg corrodes very uniformly in vivo [20,39].

In 1906, Lambotte published his experiments on pure Mg implants (99.7%) in which he used steel screws and experienced what seems to have been an electrolytic reaction resulting in the rapid accumulation of gas and sloughing out of the metal in 8 days [6,24].

Based on his observations of Mg wires in the anatomies of blood vessels, Höpfner stated that the resorption of Mg is enhanced by the movement of the external limb and that Mg resorption is reduced if the limb movement is restricted [16,38]. External limb movement was already known to enhance the local blood flow, and was speculated to have a direct effect on the local environment of the corroding Mg [16].

As a first hint of a difference between in vitro and in vivo corrosion of Mg, Lespinasse speculated that Mg corrosion in sodium chloride-rich solutions would be more rapid than in water alone [17]. Andrews found in 1917 that the total Mg absorption was dependent more on the exposed surface than on the weight of the metal [12]. This was proven by his experiments in which thin wires and sheets were absorbed faster than larger thick pieces of the same surface area [12]. All absorption was dependent on the close vital contact with living cells, and was retarded or even prevented by the presence of wound secretion, especially pus [12]. Andrews also observed inconsistent absorption of 0.05–0.45 g of pure Mg in a range of 77–100% after 14 days of implantation between the rectus muscle and the rectus sheaths in dogs.

Payr, Höpfner, Heinzhoff, McBride and Glass observed the corrosion process of Mg in blood and various tissues, but without any consistent corrosion rate [4,16,26,36,38]. Furthermore, corrosion rates varied across different animal species and tissues, though no explanation was given for this observation [38]. Seelig discovered that the degradation rate varied both with the size of the implanted pure Mg wire and with the type of tissue in which it was imbedded [11]. Seelig stated that the same amount of pure Mg corrodes slower subcutaneously (in the rabbit ear) than in more richly vascularized tissues, such as muscles. A suture of 0.007 inch diameter was placed in muscle and absorbed within 24–48 h, while a suture of 0.01 inch needed 10–14 days to be absorbed completely [11]. In contrast to Seelig's findings, Glass observed that Mg corrodes faster subcutaneously in rats compared to implantation into organs with a high circulation rate, such as the spleen of a cat [36]. Heinzhoff and Dimitroff contradicted Glass's finding, since the gas and liquid exchange around the Mg implant in parenchymatous organs should guarantee continuous transition of the oxidation products into water-soluble salts [38]. They investigated the effect of different blood flow rates in the ear vein and the spleen of rabbits on the corrosion of Mg arrows [38]. They identified further unpredictable parameters for Mg corrosion in vivo, such as limited local fluid and gas exchange, as well as autolytic changes in the blood [38]. In bone, McBride reported that 1 g of Mg–4% Al–0.3% Mn placed in the human humerus was completely absorbed in 120 days [24]. Lambotte reported that Mg plates and rods in bone were mechanically stable against finger pressure until 4 months after implantation [6]. At 6 months, the metal will be hollow and brittle, while after 9–10 months the metal osteosynthesis was dissolved without any infection or pain.

However, the binary Mg–Mn alloy exhibited the lowest corrosion rate of about 2 mg day^{-1} in subcutaneous implantation in dogs, but the industrial-grade pure Mg Domal (99.9%) exhibited similar weight loss characteristics and both corroded very homogenously in vivo [40].

7.2. Corrosion products

In 1900, Payr discussed the Mg corrosion process with his chemist colleagues who postulated that the magnesium corrosion in vivo is due to an oxidation process that is dependent on the oxygen content of the blood [3]. Furthermore, they considered (i) the local hydrogen carbonic acid content as an important factor of Mg corrosion, since magnesium carbonates could form in the corrosion layer; and (ii) the local water content of the tissue surrounding the Mg. According to Rostock [10] and Henschen and Gerlach [22], a carbonate layer was formed on the corroding Mg surface in bone which slowed down the Mg corrosion, but was dissolved after the magnesium carbonate was turned into the more water-soluble magnesium chloride. The crystalline mass found by McBride at the site of corroding Mg bone implants consisted of magnesium carbonate and magnesium phosphate [24]. Also, Hoffheinz and Dimitroff stated from their experiments that magnesium hydroxide reacts with carbonic acid to form magnesium carbonate and water at the implant surface in vivo [38].

In 1975, Fontenier et al. investigated various magnesium metals subcutaneously in dogs (Table 1) [40]. They found, regardless of the magnesium metal used, a constant composition of the corrosion layer, consisting on average of 60% phosphates of magnesium and ammonium (most likely 60% $MgNH_4PO_4 \cdot (6H_2O)$, with 20% $MgCO_3$, 10% $Mg(OH)_2$ and 10% $CaCO_3$) [40].

In 1924 Seelig discovered small particles of pure metallic Mg during early inspections after implantation, together with a soft granular detritus which he described as magnesium oxides [11]. At later wound inspections he found no vestige of Mg or its salts [11]. All corrosion products identified by Lespinasse [17] and Verbrugge [8,9] were stated as non-toxic and non-irritant. Fromherz investigated if the subcutaneous administration of Mg as a metal or hydroxide forces the elimination of calcium from the

body of rabbits [46], but did not observe any signs of elevated calcium elimination or forced decalcification of rabbit bone.

7.3. Concomitant gas formation

In 1900, Payr hypothized that hydrogen and oxygen accumulated in gas cavities in the tissue surrounding Mg implants [3,4]. Payr discovered that the gas could be fully adsorbed by the body without embolization [3,4]. Payr determined that the formation rate of gas cavities after pure Mg implantation varied, depending on the tissue type, the anatomical location and the animal model (rabbit, guinea pig) [3]. However, he never recognized gas cavities in larger animal models [3]. Höpfner reported that gas cavities from corroding intravascular Mg tubes were present only if the lumen was closed by a thrombus [16]. However, he never observed gas cavities in pulsatile arteries [16]. Lispinasse stated that 1 mg of magnesium would liberate about 1 cubic centimetre of hydrogen gas at 0 °C [17], and that the liberated hydrogen gas might have a slightly greater volume at body temperature. Lispinasse also presented Mg rings for vessel anastomosis which produced hydrogen at almost the same rate as it was resorbed. In 1924, Seelig implanted vacuum-distilled Mg strips subcutaneously into the ears of rabbits [11]. He found residues of calcinated magnesia entrapped in gas cysts. After 6 weeks, all the Mg was completely absorbed, with no gas cysts present.

Lambotte used X-rays to detect the accumulation of small gas cavities in the soft tissue surrounding Mg implants in bone [6]. He proposed that a thin hydrogen gas layer would temporarily passivate the corroding Mg alloy. McBride reported that Mg corrosion produces hydrogen and nitrogen gas in vivo, which could appear alarming in X-rays but seemed to be inert and did not create any harm due to local gas pressure [24]. The gas remained localized until it was gradually absorbed. It could accumulate in a localized cavity beneath the facia if the bony fragments were not supported by a firmly applied plaster. If the gas cavities occurred clinically, the gas had to be withdrawn by aspiration or incision [24]. McBride also reported that the tendency to create gas cavities varied with the extent to which the metal is exposed to the attack from blood serum. If the Mg oxidation is slow, as it is when the metal is well buried in cortical bone, the gas absorbs about as rapidly as it forms. If the reaction is too rapid, the gas may form a fluctuating subfacial pocket. Simple puncture or aspiration left no complications. The gas analysis of an aspirated gas pocket after 40 days of Mg band implantation by a collaborator of McBride revealed 5.6% carbon dioxide, 6.5% oxygen, 7.3% hydrogen and 80.6% nitrogen [24]. McBride explained that hydrogen absorbs as rapid as it forms, while nitrogen absorbs slowly and could form gas cavities and pressure towards the periphery [24]. This analysis and explanation remains disputable. Also, McCord et al. could not prove the theory that it is mainly hydrogen gas that is captured in the subcutaneous cavities formed by the corrosion of pure Mg and Mg–Al alloys which were implanted subcutaneously in rats [47]. Furthermore, the extensive study of an injured worker in a light metal industry led Bufe and Gissel to classify Mg injures as severe accidents, since the gas cavities produced appeared like fine cystic foam at the injury site [45].

In 1948, Troitskii and Tsitrin reported that Mg implants were hard to identify after implantation since they were radiolucent [28]. They also observed that the amount of locally evolving gas was depending on the corrosion rate of the implant, the size of the implant and the acidity of the tissue environment. After 45 days of implantation, the gas cavities disappeared. Troitski and Tsitrin recommended the use of Mg implants in open wounds and fractures since the gas could easily disappear.

8. Suggested treatments to improve corrosion behaviour of magnesium

Payr reported about the limited mechanical properties and processing routes for pure Mg at that time and recommended to use Magnalium, an alloy of aluminium with 5–50% of magnesium [3,4]. Furthermore, Seelig investigated various experimental alloy systems, such as Mg–Ce, Mg–Ca, Mg–Li and Mg–Tl [11]. He provided a list of alloying elements for binary systems (aluminium, cadmium, zinc, bismuth, antimony, silver, gold, platinum) and some ternary alloy systems (Mg–Pb–Bi and Mg–Cu–Au), which he found to be too brittle [11]. Troitskii and Tsitrin reported that the brittle character of the Mg–Cd implants could be shifted to more iron-like characteristics by adding small amounts of beryllium [28]. However, this latter approach is not recommended since beryllium is highly toxic. It should be noted that Payr, Lispinasse and other authors have emphasized the advantage of and ability to sterilize magnesium implants by boiling in hot distilled water before implantation [3,17,31]. By this procedure, they formed a dense, corrosion-protective oxide layer on their Mg parts prior to implantation. Thus, all corrosion rates given by these authors have to be handled with care. To improve the wear resistance against torsional movements, Henschen suggested immersing the implant into a solution containing 10% selenic acid and 0.5% sodium chloride for 5–15 min at room temperature [22]. The magnesium selenide which would be formed at the implant surface should be dissolved by the interstitial fluid and the hydrogen selenide formed would react with the oxygen of the tissue water to form a pore-sealing elemental selenium layer at the implant surface which should further reduce the corrosion rate. These findings were not proven in vivo by Henschen [22]. However, Rostock reported that this treatment had only little effect in vitro and no effect in vivo [10]. Delaying gas production by the use of paraffin and metallic coatings (so-called bimetallic wires) was unsuccessfully explored by Seelig [11].

9. Summary

Even though Mg and its alloys have been investigated as implants for almost two centuries, commercial implants containing Mg and its alloys are still not available. However, the advantages and obvious benefits from biodegradable metal implants are still the inspiration and hope of many researchers and clinicians. The reported historical findings should encourage more researchers and clinicians to investigate Mg and its alloys in further biomedical applications, and to explore the limitations of their clinical use. Moreover, researchers and clinicians should be warned from all the historical reports that Mg is a special lightweight metal that needs specific knowledge, careful professional handling and experience-based design to be a successful biomaterial.

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References

[1] Kammer C. Magnesium Taschenbuch. Düsseldorf: Aluminium-Verlag; 2000.
[2] Huse EC. A new ligature? Chicago Med J Exam 1878:172-2.
[3] Payr E. Beiträge zur Technik der Blutgefäss- und Nervennaht nebst Mittheilungen über die Verwendung eines resorbirbaren Metalles in der Chirurgie. Arch Klin Chir 1900;62:67–93.
[4] Payr E. Blutgefäß- und Nervennaht (nebst Mittheilung über die Verwendung eines resorbirbaren Metalles in der Chirurgie). Centralblatt für Chirurgie

1901;28(Beilage: Bericht über die verhandlungen der deutschen Gesellschaft für Chirurgie, XXIX Kongress, abgehalten vom 18.-21. April 1900 im Langenbeck-Hause); p. 31–37.
[5] Lambotte A. Technique et indications de la prothèse perdue dans la traitement des fractures. Presse Med Belge 1909;17:321–3.
[6] Lambotte A. L'utilisation du magnésium comme matériel perdu dans l'ostéosynthèse. Bull Mém Soc Nat Cir 1932;28:1325–34.
[7] Verbrugge J. La tolérance du tissu osseux vis-à-vis du magnésium métallique. Presse Med 1933;55:1112–4.
[8] Verbrugge J. Le matériel métallique résorbable en chirurgie osseuse. Presse Med 1934;23:460–5.
[9] Verbrugge J. L'utilisation du magnésium dans le traitement chirurgical des fractures. Bull Mém Soc Nat Cir 1937;59:813–23.
[10] Rostock P. Ist das Magnesium als Naht- und Schienungsmaterial für Knochenoperationen geeignet? Arch Orthop Trauma Surg 1937;38(3):486–92.
[11] Seelig MG. A study of magnesium wire as an absorbable suture and ligature material. Arch Surg 1924;8(2):669–80.
[12] Andrews EW. Absorbable metal clips as substitutes for ligatures in wound closure. JAMA 1917;28:278–81.
[13] Gossrau G, inventor I.G. Farbenindustrie Akt.-Ges. in Frankfurt, Main, assignee. Nähmaterial aus Magnesiumdrähten für chirurgische Zwecke. Germany; 1935.
[14] Jorgensen R. Bio-absorbable metal hemostatic clip. US patent 4.602.632, 29 July 1986.
[15] Vordemann S. Ueber die Resorption von Magnesium und Magnesium-Zirkoniumfäden unter Berücksichtigung der bisherigen Anwendung von Magnesium zu chirurgischen Zwecken. Göttingen: Georg-August-Universität zu Göttingen; 1939.
[16] Höpfner E. Ueber Gefässnaht, Gefässtransplantation und Replantation von amputirten Extremitäten. Arch Klin Chir 1903;70:417–71.
[17] Lespinasse VD. A practical mechanical method of end-to-end anastomosis of blood-vessels: using absorbable magnesium rings. JAMA 1910;55:1785–90.
[18] Hermawan H, Dube D, Mantovani D. Developments in metallic biodegradable stents. Acta Biomater 2010, this issue.
[19] Stone P, Lord Jr JW. An experimental study of the thrombogenic properties of magnesium and magnesium–aluminum wire in the dog's aorta. Surgery 1951;30(6):987–93.
[20] Payr E. Zur Verwendung des Magnesiums für resorbirbare Darmknöpfe und andere chirurgisch-technische Zwecke. Centralblatt Chir 1901;28(20): 513–5.
[21] Chlumský V. Über die Wiederherstellung der Beweglichkeit des Gelenkes bei Ankylose. Centralblatt Chir 1900;27(37):921–5.
[22] Henschen C, Gerlach W. Spektrographische Untersuchungen über die von metallischen Fremdkörpern (Allenthesen) ausgehenden Metallosen der Gewebe, besonders der Knochen. Zentralblatt Chir 1934;61(14):828–37.
[23] Groves E. An experimental study of the operative treatment of fractures. Br J Surg 1913;1(3):438–501.
[24] McBride ED. Magnesium screw and nail transfixion in fractures. South Med J 1938;31(5):508–15.
[25] Zierold AA. Reaction of bone to various metals. Arch Surg 1924;9(2):365–412.
[26] McBride ED. Absorbable metal in bone surgery. JAMA 1938;111:2464–7.
[27] Maier O. Über die Verwendbarkeit von Leichtmetallen in der Chirurgie (metallisches Magnesium als Reizmittel zur Knochenneubildung). Deut Z Chir 1940;253:552–6.
[28] Троицкий ВВ, Цитрин ДН. Рассасывающийся металлический сплав „остеосинтезит" как материал для скрепления кости при переломах. Хирургия 1948;8:41–4.
[29] Stroganov G, Savitsky E, Tikhova N, Terekhova VF, Volkov MV, Sivash KM, et al. Magnesium-base alloy for use in bone surgery, US patent 3,687,135, 29 August 1972.
[30] Hume-Rothery W, Bowell SW. The system magnesium–cadmium. Institute of Metals – advance paper 1927(445); 18 pp.
[31] Payr E, Martina A. Experimentelle und klinische Beiträge zur Lebernaht und leberresection (Magnesiumplattennaht). Arch Klin Chir 1905;77(4):962–98.
[32] Payr E. Ueber Verwendung von Magnesium zur Behandlung von Blutgefässerkrankungen. Deut Z Chir 1902;63:503–11.
[33] Payr E. Zur Technik der Behandlung kavernöser Tumoren. Zentralblatt Chir 1903;30:233–4.
[34] Payr E. Weitere Erfahrungen über die Behandlung von Blutgefäßgeschwülsten mit Magnesiumpfeilen. Zentralblatt Chir 1905;49:1335–8.
[35] Sonntag E. Die Hämangiome und ihre Behandlung. Ergebn Chir Orthop 1914;8: 1–156.
[36] Glass E. Klinische und experimentelle Untersuchungen über die Payrsche Magnesiumpfeilbehandlung von Angiomen. Deut Z Chir 1926;194(5–6): 352–66.
[37] Wilflingseder P, Martin R, Papp C. Magnesium seeds in the treatment of lymph- and haemangiomata. Chir Plastica 1981;6:105–16.
[38] Hoffheinz S, Dimitroff N. Experimentelle Studie über die resorption parental zugeführten metallischen Magnesiums. Deut Z Chir 1928;208: 346–53.
[39] Chlumský V. Beiträge zur Darmknopffrage. Mitt Grenzgebieten Med Chir 1907;3:416–51.
[40] Fontenier G, Freschard R, Mourot M. Study of the corrosion in vitro and in vivo of magnesium amodes involved in an implantable bioelectric battery. Med Biol Eng 1975;13(5):683–9.
[41] Wexler BC. Pathophysiologic responses of spontaneously hypertensive rats to arterial magnesium–aluminum wire implants. Atherosclerosis 1980;36(4): 575–87.
[42] Nogara G. Sulla tolleranza dell' osso verso i metalli riassorbibili magnesio ed electron. Arch Ital Chir 1939;56(5):459–78.
[43] Nicole R. Metallschädigung bei Osteosynthesen. Hel Chir Acta 1947;14(Suppl. III(2)):3–74.
[44] Hussl H, Papp C, Höpfel-Kreiner I, Rumpl E, Wilflingseder P. Resorption time and tissue reactions with magnesium rods in rats and rabbits. Chir Plastica 1981;6:117–26.
[45] Bufe W, Gissel H. Die experimentellen Grundlagen der Leichtmetallverletzungen. Deut Z Chir 1939;252:224–32.
[46] Fromherz K. Über die Resorption des parenteral beigebrachten metallischen Magnesiums und dessen Einfluß auf den Kalkstoffwechsel. Z Chir 1909:210–30.
[47] McCord CP, Prendergast JJ, Meek SF, Harrold GC. Chemical gas gangrene from metallic magnesium. Ind Med 1942;11(2):71–6.