Biomaterials Highlights II

Materials for Biomedical Applications – High Long-Term Success Rates Might Pose New Problems**

By Günther Heimke*

The main influences on the survival rate of implants for a given purpose are:

- the implantation technique and the skill of the surgeon
- the implant material or materials
- the shape of the implant

At a first approximation, the second and third influences are typical engineering aspects. However, as the size, the shape, and the stiffness of an implant can influence the operational procedure, the implantation technique might also be influenced by engineers.

All three major groups of solids have been considered or are used as implant materials: organic solids (like plastics, textiles, even wood, but also ivory and other animal hard tissue) metals, and ceramics.

Plastics are widely used in soft tissue replacements and have stood the test of several decades of service in such different applications as resorbable and non-resorbable sutures, vascular grafts, intraocular lenses, and in many areas of corrective surgery. Their most common applications in orthopedic surgery are the polyethylene sockets in total hip replacements, inlays on the tibial components of total knee protheses and the polymethylmethacrylate (PMMA) bone cement.

The main metallic implant materials are the stainless steels, the Co–Cr–Mo alloys, and some titanium alloys. Today, the application of the stainless steels is essentially confined to temporary implants like bone plates and screws, intramedullary rods, and pins and wires because of their relatively high corrosion rate[1] (more than 75% of all retrieved stainless steel components show evidence of pitting and crevice corrosion). The Co–Cr–Mo alloys have increasingly replaced the stainless steels in all long term (if possible life long) applications like joint replacements and dental implants. In the latter field, these Co based alloys have been substituted almost completely by titanium and some of its alloys. In joint replacements, titanium alloys are also gaining ground.

In spite of being the oldest man made material, the ceramics have been the last group of materials to be considered and tested for implant purposes.[2] Some essentially bioinert oxide ceramics, in particular the highly pure and dense version of alumina ceramic, have found widespread applications for the articulating components in total joint replacements[3] and as dental implants.[4] The fascinating ability of some Ca-phosphate based ceramics, glasses and glass-ceramics (socalled bioactive ceramics) to form a strong bond to bony tissue has not yet be exploited for the fixation of load bearing implants because of the relatively poor mechanical strength and the instability of these materials in the body environment. Trials to overcome these problems by combining them with high strength metals are presently under way.

All of the well established implant materials have stood the test of short and, with the exception of the stainless steels, medium term clinical applications. They have contributed to the considerable increase of survival times and allowed for the use of such devices in younger and younger patients. This, in turn, necessitates the extension of the time of reliable service of all components of such implant systems to much more than ten years. However, all of these implant materials release some matter into their environment.

The presently used plastics and in particular their wear debris have been kept under careful observation without resulting in any alarming finding beyond their influence on the formation and widening of the radiolucencies along adjacent PMMA to bone interfaces. The destruction of the polyethylene sockets of total hip replacements by wear and cold working can be partially counteracted by the use of alumina ceramic for the heads instead of metal.[5] The contribution of the aging of the PMMA bone cement to the increases of the failure rates of total joint replacements has been the main motivation for the attempts to find other modes of implant fixation.

A carcinogenicity test on alumina ceramic was commenced together with the early compatibility studies of this material and proved negative.[6] No reports are yet available which would allow any judgment on medium or long term systemic effects of the bioactive ceramics to be made.

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There is, however, some concern about the long term systemic effects of the corrosion products from metals. Their corrosion rates are estimated to be 0.15 to 0.3 microgram/ cm^2/day[7,8] or about 11 to 22 mg/year for a typical total hip prosthesis. This was confirmed in a paper[9] presented at the recent US Biomaterials Conference. In 24 patients with an average implantation time of 9.8 years, total metal concentrations ranging from 2.6 to 248 microgram/g of dry tissue with an average of 35 microgram/g were found. (For comparison, the total body burden of an average person is less than 10 mg with concentrations in the order of 0.1 nanogram/g.[10])

Table 1. The incidence of different kinds of cancer in patients with total hip replacements in comparison to the average population (summarized from [11]), expressed as the ratio of (cases observed in this study)/(cases expected in the average population).

follow-up in years	person years	all	Type of Cancers (ICD): breast (174)	colon & rectum (153 & 154)	bronchus & lung (162)	lymphatic & haemopoietic systems (200 to 208)
Less than 1	1328	1.31	–	0.31	0.71	5.26 +
1 to 2	1293	0.46*	–	–	0.93	–
2 to 5	3687	0.61 +	0.24	0.38*	1.16	1.62
5 to 10	5330	0.77*	0.30*	0.52*	0.54	1.38
Over 10	2648	1.60 +	1.01	1.48	1.51	1.66
Total	14286	0.91	0.36 +	0.62*	0.92	1.68*
0 to 10		0.74 +	0.22 +	0.41 +		

* p 0.05, + p 0.01

Of course, the biological effects of the metals used in these alloys differ considerably. Traces of some of them are even needed in normal metabolism, like cobalt in vitamin (B_{12}) synthesis. The concentrations mentioned above, however, are far beyond such limits. Allergies to some of the metals, in particular nickel, cobalt, and chromium, are known and can be avoided by using titanium based materials. Titanium actually is the only metal with a record of several decades of clinical application during which no adverse effects have been reported in spite of the fact that sometimes considerable accumulations of fine Ti particles are seen in the vicinity of such implants.

Until now, there have been not more than ten reports of the occurance of tumors in direct relation to orthopedic implants, but three were published in 1986 and 1987 alone. With the extension of the survival times to the 15 and even 20 years region, information from the epidemiology of human workplace exposure to metal-bearing chemicals and other possible carcinogens with latencies in this order of magnitude must be considered.[10] In the same issue, a group from New Zealand reported on a statistical evaluation of the records of 1358 patients who had received total hip replacements between 21 and 15 years earlier.[11] Using the data of the New Zealand Cancer Registry, they could identify which of these 1358 individuals had developed malignant tumors and compare these numbers with the average rate of tumor occurance in this population. For 298 individuals no data could be made available. They were assumed in the main analysis to be healthy survivers. Table 1 shows the results of this evaluation which is based on a total of 14286 person-years.

Generally, a significant decrease in overall cancer incidence up to ten years after operation and a significant increase in those followed for longer than 10 years can be seen. This initial decrease was no longer significant if the 298 individuals of uncertain status at the end of the study were removed from the evaluation.

There is, however, a significant increase overall in the incidence of tumors of the lymphatic and haemopietic systems. The cumulative effect remained significant through the entire study. If the tumors observed in the first two years were excluded, the increase in incidence in the remainder of the study period persisted, but decreased in significance (16/10.57 = 1.51, p = 0.07). The diagnosis for the total hip replacements in these 21 patients was 17 cases of osteoarthritis, two rheumatoid arthritis, and one each with idiopatic aseptic necrosis and Paget's desease.

After discussing many factors which might have influenced their results, the authors point to the fact that the risk of developing a lymphoreticular neoplasm remains small, increasing from 2 per 1000 in the normal population to 6 per 1000 in the study group over 10 years. Nevertheless, the long term biological effects of implants definitly require more detailed attention as their survival times increase.

Along the lines of this warning an Editorial in the January 1989 issue of the British Journal of Bone and Joint Surgery asked its readers to report all cases of malignant tumors along with the necessary details in order to find out if the ten cases reported until now may just be the tip of an iceberg. In addition, animal experiments are presently underway attempting to quantify serveral parameters in order to allow for a more reliable judgement on the risks and to provide possible recommendations to cope with these problems.

[1] S. D. Cook, *Clin. Orthop. 194* (1985) 236.
[2] G. Heimke, *Adv. Mater. 1989* 7; *Angew. Chem. Int. Ed. Engl. 28* (1989) 111; *Angew. Chem. 101* (1989) 113.
[3] P. Griss, G. Heimke in D. F. Williams (Ed.): *Biocompatibility of Clinical Implant Materials*, Vol. 1, CRC-Press, Boca Raton, FL 1981, p. 155.
[4] W. Schulte, *Zahnärztl. Mitt. 71* (1981) Issues 19 and 20.
[5] M. Semlitsch, M. Lehmann, H. Weber, E. Dörre, H.-G. Willert, *J. Biomed. Mater. Res. 11* (1977) 537.
[6] P. Griss, E. Werner, R. Buchinger, C. M. Büsing, G. Heimke, *Arch. Orthop. Unfall-Chir. 90* (1977) 29.
[7] S. G. Steinemann in G. D. Winter, J. L. Leray, K. de Groot (Eds.): *Evaluation of Biomaterials*, Wiley, Chichester 1980, p. 1.
[8] S. G. Steinemann, in A. Luterjering, U. Zwicker, W. Bunk (Eds.): *Titanium, Science and Technology*, Vol. 2, Deutsche Gesellschaft für Metallkunde, Berlin 1985, 1373.
[9] F. Betts, K. K. Hansraj, M. Bansal, T. W. Wright, Transactions of the 15th Annual Meeting of the Society for Biomaterials, April 28–May 2, 1989, 145.
[10] J. Black, *J. Bone Jt. Surg. Br. 70-B* (1988) 517.
[11] W. J. Gillespie, C. M. A. Frampton, R. J. Henderson, P. M. Ryan, *ibid.* 539.

Conference Reports

Magnetism in Washington

By Frans Greidanus *

The 1989 INTERMAG (International Magnetics Conference, Washington, USA, March 28.–31.) provided a forum for engineers and scientists to discuss the field of magnetics, from basic research to applications. The sessions included invited and contributed papers, poster sessions, workshops and tutorials. The total number of participants was approximately 800. The diversity of the field was indicated by presentations covering all branches of magnetics and related technologies. Topics discussed included recording heads, superconductivity, microwave components, numerical techniques and field calculations, hard magnets, amorphous magnets, magnetic measurements, recording systems, coercivity mechanisms, domains and domain walls, magneto-optics, magnetic separation and biomagnetism, thin film media, soft magnetic materials, perpendicular recording, and bubble and bloch line memories. Most of the conference took place in six parallel sessions. In the plenary session on March 29. Professor *Iwasaki* from Tohoku University was awarded the 1989 Cledo Brunetti Award for his contributions to the miniaturization of magnetic recording systems.

Also on March 29. a workshop on scanning electron microscopy with polarization analysis (SEMPA) was organized by *J. Unguris* from the National Institute of Standards and Technology (formerly called NBS). SEMPA is a relatively new technology which enables high resolution imaging of magnetic domains by the analysis of the polarization state of electrons reflected from a magnetic surface. In general there was much interest in magnetic domain imaging and related new techniques. Another new tool in this field is the magnetic force microscope. Its possibilities were reviewed in an excellent paper by *Rugar, Mamin, Stern, Fontana, Kasiraj, McFadyen* and *Lambert* from IBM and optical imaging techniques were reviewed in a paper by *Argyle*, also from IBM.

Materials played an important role at the 1989 INTERMAG conference. Examples are Ba-ferrite as a promising new magnetic recording material, the use of magnetic Co/Pt multilayers for magneto-optical recording, and the application of NdFeB permanent magnets in magnetic imaging devices for clinical applications using NMR.

A substantial number of papers dealt with magnetic recording. Of these about 100 were devoted to magnetic recording, and about 40 to magneto-optical recording. On March 28. a symposium on the status and future of magnetic and magneto-optical disk-drive technologies was organized by Professor *M. Kryder* from Carnegie Mellon University. In this symposium *G. Hughes* (Seagate), *F. Greidanus* (Philips), *D. Rugar* (IBM) and *T. Toshima* (NTT) presented their views. Magneto-optical recording will find its place in the market, but the question whether it will (partially) replace Winchester technology remains to be answered.

An important issue in magneto-optical recording is "direct overwrite." Papers by *Nakao, Sukeda, Ojima, Taka* and *Nishiyama* (Hitachi) and *Greidanus, Jacobs, Spruit* and *Klahn* (Philips) discussed the field-modulation technique. *Kryder, Shieh, Schultz* (Carnegie Mellon), *Meiklejohn* and *Skoda* (MOVID Information Technology) showed real time movies of the writing and erasing of domains with a single laser, operating under different conditions. *Van den Berg* and *Röckelein* (Siemens) proposed two new "direct overwrite" schemes, employing two magnetic layers separated by a thermal insulating layer. It is clear that this subject will attract more attention in the coming years.

Kano, Shono, Kuroda, Koshino and *Ogawa* (Fujitsu) reviewed the possibilities of sputtered garnets for future applications in magneto-optical disks. With garnet layers deposited on Gandolinium Gallium Garnet (GGG) single crystals

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