When choosing between the materials of metal implants the surgeon needs to balance the pros and cons mainly of steel and titanium. The present paper elucidates the practical aspects based on the complex scientific background that has identified the differences between the two metals in their electrochemical and biological behavior. The data presented here are intended to help the surgeon when he is confronted with different and often complex clinical situations and problems.

The following case from the ICUC database, where a titanium plate was implanted into a flourishing infection, represents the clinical experience leading to preferring titanium over steel and internal fixator over conventional plates. (Fig. 1) (1)

Current opinions regarding biological aspects of implant function.

The "street" opinions regarding the biological aspects of the use of steel versus titanium as a surgical trauma implant material differ widely. Statements of opinion leaders range from "I do not see any difference in the biological behavior between steel and titanium in clinical application" to "I successfully use titanium implants in infected areas where steel would act as foreign body "sustaining" infection." Furthermore, some comments imply that clinical proof for the superiority of titanium in human application is lacking. The following tries to clarify the issues addressing the different aspects more through a practical clinical approach than a purely scientific one, this includes simplifications.

Today's overall biocompatibility of implant materials is accepted but. As the vast majority of secondary surgeries are elective procedures this allows the selection of implant materials with optimal tissue tolerance and infection resistance. The different biological reactions of stainless steel and titanium are important for this segment of clinical pathologies. Biological tolerance (2) depends on the toxicity and on the concentration of soluble implant material released. The local concentration of the corrosion products depends on release, diffusion and washout through blood circulation. Alloying components of steel, especially nickel and chromium, are less than optimal in respect to tissue tolerance and allergenicity. Titanium as a pure metal provides excellent biological tolerance (3,4,5,6). Improved strength was obtained by titanium alloys like TiAl6V4. The latter found limited application as surgical implants. It contains Vanadium (7). Today's high strength titanium alloys contain well tolerated alloying components² like Zr, Nb, Mo and Ta (ISO 5832-14) (8,9).

The corrosion rate of surgical implants is kept low by the passive layer formed when immersed in body fluids (10,11). The passive layer may be locally destroyed, for instance, by mechanical fretting or by local corrosion conditions like in pitting; it is renewed by an electrochemical corrosion process which releases alloying components like Ni and Cr (Fig. 2) (12). The amount of soluble component may vary markedly depending on the local electrochemical conditions (see below).

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1 This is part 2 of 2, part one deals with the mechanical aspects. ICUC® App (www.icuc.net).
2 With the exception of TiAl6V4 which contains with Vanadium (6) a toxic element tolerated due to very small release.
Fig. 1: Absent foreign body effect: Double titanium plates used for stabilization of a flourishing S. aureus infected re-osteosynthesis. 17 weeks later, the wound is healed. How would the picture look after steel implantation?

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Fig. 2: Scratching destroys the passive layer. Within minutes the passive layer is rebuilt. This process releases corrosion products. Steel and titanium differ in respect to speed of reformation of the passive layer (12)
Adhesion, mechanical irritation, capsule formation and dead space

The adhesion of surrounding tissues onto the implant surface (13) plays an important role in respect to resistance to infection. When the tissues do not attach initially the displacement between moving tissues and implant is concentrated within the interface at the surface of the implant where a dead space forms (Fig. 3). The large displacement within the small distance results in irritating large strain. A dead space filled with fluid results which impedes infection resistance. Without adherence mechanical irritation induces formation of a capsule that encompasses a dead space (Fig. 4) The capsule diminishes the access of cells defending infection and favors growth and the propagation of bacteria.

Fig. 3: The importance of initial tissue adherence in respect to capsule formation and deleterious dead space around the implant. ABOVE: discontinuous tissue deformation. When the tissue does not adhere to the implant a zone of high strain produces mechanical irritation and a dense capsule and a dead space develops. BELOW: when the tissue adheres from beginning on the soft tissue takes the deformation gradually, no discontinuity, no dead space, good resistance to infection.

Fig. 4: Schematic representation of the dead space issue: LEFT: when tissue does not adhere. The dense capsule, a result of mechanical irritation, prevents access of the mobile defense. It also allows growth and spreading of bacteriae. RIGHT: When tissue adheres no capsule formation, bacteria cannot spread and the mobile defense has good access through the less poriferous tissue.
In the ideal case a soft granulation tissue attaches to the implant immediately after implantation, providing a soft, continuous bridge from implant to moving tissue \(\text{(Fig. 3)}\). Then the bridging tissue stiffens and the increasing adherence maintains the contact and avoids dead space. This is a situation where titanium stands out in its support of infection resistance. Whether a tissue adheres depends on strength of contact between tissue and implant and on the of peeling\(^3\) force applied. The adherence may be very strong whereby the tissue adhering to the implant resists the large forces applied by peeling \(\text{(Fig. 5)}\).

**Different types of corrosion**

When a bulk material of steel or titanium is immersed in biological fluids the corrosion rate of both intact materials is very low due to the protection offered by the passive layer. Once scratching destroys the passive layer locally the two materials behave differently. Steel is very sensitive to discontinuities in the local electrochemical environment. Fretting and/or crevices may produce a local condition such as pits\(^4\) that maintains corrosion. When corrosion attack produces a small pit the local lack of oxygen in the pit or in a crevice may prevent passivation and the local conditions maintain a hundred-fold rate of corrosion compared to bulk material \(\text{(Fig. 6)}\). Titanium is not subject to similar conditions of corrosion except at extremely low pH. When an implant like a plate-screw becomes loose mechanical abrasion between plate and screws arise. The passive layer will be repeatedly destroyed. Even today in such a situation appreciable corrosion in steel may result \(\text{(Fig. 6)}\). Mechanical abrasion is different; in titanium it may form inert metallic deposits \(\text{(Fig. 7)}\).

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\(^3\) The term peeling includes here classical peeling (pulling away) and displacement along the surfaces (shear).

\(^4\) Within a pit for instance low oxygen needed for formation of the passive layer, or lower pH may favor local corrosion of steel.
Biocompatibility testing, our experience at the AO Research Institute

Biocompatibility testing in vitro
Tissue or bone organ cultures were used for preliminary screening tests (3,4). In organ culture bone rudiments were cultivated whereby soluble metal salts were added to the culture medium or where small metal pins were inserted into the bone rudiments. The length of the epiphysis was used as a parameter of growth. (Fig. 8)

Biocompatibility in animals
Biological compatibility of different implant materials has been widely tested in animals. Because mechanical irritation through movement of the tissues in relation to the implant surface results in cellular reaction, the shape of the implant plays an important role (4). A small cylindrical implant will experience mechanical irritation while the so called "Davos implants" that meet ISO standards provide a segment of contact which is protected from mechanical irritation (Fig. 9, Fig. 10).

Fig. 8: Organ culture testing toxicity of metal salts. The results of different metal salts (3,4). Vanadium is more toxic than nickel and cobalt. It impedes growth at 10x smaller concentration

Fig. 9: Testing biocompatibility using "Davos" cylinders eliminating artefacts due to mechanical irritation. The tissue between the grooves is stably connected and artefacts avoided (5).
Biocompatibility in humans

The sampling of tissues at implant removal allows observation of the presence of blood vessels and cells at different distances from the implant. While the amount of round cells is similar, all the other elements of tissue reaction show important differences between steel and titanium implants in favor of titanium (Fig. 11) [6].

Fig. 10: The tissue reaction to steel and titanium cylinders at 1, 3 and 9 weeks observation. Mechanically stabilized interface. Good acceptance of both bulk materials [5].

Fig. 11: Human biopsies from steel and titanium at different distances from the implants. The macrophages shows a large count in steel; the small vessels are more prominent in titanium [6]. Titanium is superior.
Testing systemic allergy through observation of leucocyte migration
It is today accepted that 25% of young female persons react to skin contact with nickel. Allergic reactions to implanted material containing nickel are less frequent. With this difference in mind patch testing is of limited value when selecting an implant material. Therefore, a test that measures systemic changes was used. The migration of leucocytes reacts very sensitively to systemic immunological reactions (14). The effect of corrosion products on the migration of the blood cells was observed. The so-called Leucocyte Migration Test provides information on systemic reactions (Fig. 12) (14). Unfortunately, the migration test does not lend itself to reliable prognosis.

Clinical observation
The testing of leucocyte migration in a patient with a steel implant was revealing. The patient, a medical doctor, repeatedly reported uneasiness with the implants used for stabilization of his malleolar fracture. Several blood tests with steel implants in place showed suppressed leucocyte migration. When the steel implants were removed, uneasiness subsided and the migration recovered to normal (Fig. 13) (15). We do not know of titanium allergy reported under conditions excluding all other allergens.

Infection
The superior infection tolerance observed with titanium implants has been repeatedly documented in animals (16, 17), (Fig. 14) and also in humans (6). Several surgeons switching from steel to titanium stated that for titanium implants implanted into infected areas the problems observed with steel were absent (18, 19).

Fig. 12: Leucocyte migration test. Left control: the cells migrate from the buffy coat below; Right: in a medium containing nickel, migration is inhibited (14).
Combined use of steel and titanium implants.

Because of shortage of one of the materials but also to take advantage of the different characteristics of steel and titanium like the problem of galling mentioned above, it may make sense to combine steel and titanium implants, because each metal when submersed in a conducting fluid (like Ringers) undergoes polarization resulting in a material-specific electric resting potential. If two different materials are submersed and electrically connected, be it by contact or wired, the difference in the resting potential gives rise to an electric current corroding the one with the higher positive resting potential. The electrical isolation of titanium prevents galvanic corrosion (no current no corrosion no release). Rüedi (20) as well as Wächtler (21) demonstrated that steel screws applied to titanium plates do not produce galvanic corrosion and are tolerated as steel alone without diminishing the advantage of titanium biocompatibility.

![Fig. 13: Leucocyte migration before and after removal of steel implants. Suppressed migration and pain before implant removal (15).](image)

![Fig. 14: Infection rate related to inoculum doses (CFU). The numbers indicate the number of infected and the total number of animals at each inoculum dose. Superior result with titanium (17).](image)
Conclusions
Titanium is a biologically superior implant material; its performance in infected cases is clinically relevant. The difference is explained by evidence of a minimal systemic reaction as revealed by the leucocyte migration test. The absence of relevant allergy seems to play an important role. Tissue adherence to titanium, facilitated by the biocompatibility of the material and surface structure, avoids formation of dead space, which promotes the deleterious propagation of bacteria. Formation of a dense capsule through mechanical irritation within a zone of displacement impedes access of mobile defense and disables secondary re-attachment. The advantage of soft tissue adherence may be unfavorable when bone adheres to titanium resulting in difficult implant removal. We do not expect a single improvement to resolve all problems, but the way to an optimal implant is paved with research contributions and careful clinical consideration of an optimal balance between pros and cons.
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