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Current Concepts Review

Corrosion of Metal Orthopaedic Implants*

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In situ degradation of metal-alloy implants is undesirable for two reasons: the degradation process may decrease the structural integrity of the implant, and the release of degradation products may elicit an adverse biological reaction in the host. Degradation may result from electrochemical dissolution phenomena, wear, or a synergistic combination of the two. Electrochemical processes may include generalized corrosion, uniformly affecting the entire surface of the implant, and localized corrosion, affecting either regions of the device that are shielded from the tissue fluids (crevice corrosion) or seemingly random sites on the surface (pitting corrosion). Electrochemical and mechanical processes (for example, stress corrosion cracking, corrosion fatigue, and fretting corrosion) may interact, causing premature structural failure and accelerated release of metal particles and ions.

The clinical importance of degradation of metal implants is evidenced by particulate corrosion and wear products in tissue surrounding the implant, which may ultimately result in a cascade of events leading to periprosthetic bone loss. Furthermore, many authors have reported increased concentrations of local and systemic trace metal in association with metal implants^{1,4,5,9-11,14,18,25,26,28,29,47,49-55,58,71,72,75-77,87,90,108-110}. There also is a low but finite prevalence of corrosion-related fracture of the implant.

This review focuses on electrochemical corrosion phenomena in alloys used for orthopaedic implants. A summary of basic electrochemistry is followed by a discussion of retrieval studies of the response of the implant to the host environment and the response of local tissue to implant corrosion products. The systemic

implications of the release of metal particles also are presented. Finally, future directions in biomaterials research and development with regard to corrosion processes are considered.

General Concepts Related to Corrosion

Corrosion of orthopaedic biomaterials is a complex multifactorial phenomenon that depends on geometric, metallurgical, mechanical, and solution-chemistry parameters, and a firm understanding of these factors and their interactions is required in order to comprehend how and why implant materials corrode. In this section, the basic electrochemistry of corrosion and the interactions that occur between material, mechanical, and solution-chemistry parameters in orthopaedic alloys *in situ* are described.

Two essential features determine how and why a metal corrodes. The first characteristic involves thermodynamic driving forces, which cause corrosion (oxidation and reduction) reactions, and the second involves kinetic barriers, which limit the rate of these reactions. The thermodynamic driving forces that cause corrosion correspond to the energy required or released during a reaction. The kinetic barriers to corrosion are related to factors that impede or prevent corrosion reactions from taking place. The basic underlying reaction that occurs during corrosion is the increase of the valence state — that is, the loss of electrons — of the metal atom to form an ion, as expressed by the equation: $M \rightleftharpoons M^{n+} + ne^-$. This oxidation event may result in free ions in solution, which then can migrate away from the metal surface or can lead to the formation of metal oxides, metal chlorides, organometallic compounds, or other chemical species. These latter forms may be soluble or may precipitate out to form solid phases. The solid oxidation products may be subdivided into those that form adherent compact oxide films and those that form non-adherent oxide, chloride, phosphate, or other particles that can migrate away from the metal surface. In all of these possible reactions, there is a thermodynamic driving force for the oxidation of metal atoms to their ionic form. In this case, the driving force is the free energy (ΔG) resulting from these reactions, which can be calculated with use of the equation⁸⁰:

$$\Delta G_{red} = \Delta G^\circ + RT \ln \frac{[M]}{[M^{n+}][e^-]^n}$$

where ΔG_{red} is the free energy for the reduction reaction,

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ΔG° is the free energy of the reaction in a defined standard state, R is the gas constant, T is the temperature, and the bracketed values are the activities (or the approximate concentrations) of the species involved in the reaction. If ΔG is greater than zero, then the reduction process requires energy or, alternatively, the oxidation process releases energy and will occur spontaneously.

In general, there are two sources of energy to be considered in corrosion processes. The first is a chemical driving force that determines whether corrosion will take place under certain conditions. If the free energy for oxidation is less than zero, then oxidation will occur spontaneously, as in the metals in the alloys used for orthopaedic implants. The second source of energy occurs when positive and negative charges (metal ions and electrons, respectively) are separated from one another during corrosion. The ions are released into solution or go on to form an oxide or another compound, and the electrons are left behind in the metal or undergo other electrochemical reactions, such as reduction of oxygen or hydrolysis of water. This separation between the charges contributes to what is known as the electrical double layer and creates an electrical potential across the metal-solution interface (much like a capacitor), as expressed by $\Delta G = -nF\Delta E$, where n is the valence of the ion, F is the Faraday constant, and ΔE is the voltage or potential across the interface between the metal and the solution. This potential is a measure of the reactivity of the metals or the driving force for metal oxidation. The more negative the potential of a metal in solution, the more reactive it will tend to be.

At equilibrium, the chemical energy balances with the electrical energy, yielding the Nernst equation^{3,57}:

$$\Delta E = \Delta E^\circ + \frac{RT}{nF} \ln \frac{[M^{n+}]}{[M]}$$

which states that there is an electrical potential across the interface between the metal and the solution when metals are immersed in a solution.

From this equation, a scale of reactivity of the metal, known as the electrochemical series, can be established⁴³. This scale ranks the equilibrium potential from most positive (least reactive, or most noble) to most negative (most reactive, or most base). This ranking is based only on thermodynamic considerations — that is, if it is assumed that there is no barrier to the oxidation of the metal, these are the potentials across the metal-solution interface. Certain metals owe their resistance to corrosion to the fact that their equilibrium potentials are very positive, indicating that the chemical driving force for oxidation either is very small and negative or is positive (Table I). Therefore, there is little or no driving force for oxidation unless the potentials of these materials are raised well above their equilibrium potentials. Gold and platinum are examples of metals that have little or no driving force for oxidation in aqueous solutions; hence, they tend to remain in metallic form

TABLE I
STANDARD ELECTROCHEMICAL SERIES FOR SELECTED METALS^{43*}

	Reaction		Potential (Volts)
Noble	Au ³⁺ + 3e ⁻	⇌ Au	1.42
	Pt ²⁺ + 2e ⁻	⇌ Pt	1.20
	Ag ⁺ + e ⁻	⇌ Ag	0.80
	O ₂ + 2H ₂ O + 4e ⁻	⇌ OH ⁻	0.40
	Ti(OH) ³⁺ + H ⁺ + e ⁻	⇌ Ti ³⁺ + H ₂ O	0.06
	H ⁺ + e ⁻	⇌ 1/2 H ₂	0.00
	Fe ³⁺ + 3e ⁻	⇌ Fe	-0.04
	Co ²⁺ + 2e ⁻	⇌ Co	-0.28
	Fe ²⁺ + 2e ⁻	⇌ Fe	-0.41
	Cr ²⁺ + 2e ⁻	⇌ Cr	-0.56
	Cr ³⁺ + 3e ⁻	⇌ Cr	-0.74
	2H ₂ O + 2e ⁻	⇌ 2OH ⁻	-0.83
	TiO ₂ + 4H ⁺ + 4e ⁻	⇌ Ti + 2H ₂ O	-0.86
	Ti ²⁺ + 2e ⁻	⇌ Ti	-1.60
Mg ⁺ + e ⁻	⇌ Mg	-2.37	
Active	Na ⁺ + e ⁻	⇌ Na	-2.71

*These values are based on the standard hydrogen electrode scale. The more noble metals (at the top of the list) are less reactive, while the more active metals (toward the bottom) are more reactive and have a higher driving force for oxidation (corrosion). Note that titanium and chromium (particularly the trivalent form) are both very reactive and have a high driving force for oxidation.

indefinitely in the human body. However, metals that are commonly used in orthopaedics have more negative potentials, indicating that, from a chemical driving-force perspective, they are much more likely to corrode. For example, titanium has a very large negative potential (Table I), indicating a large chemical driving force for corrosion (oxidation). If some other process such as passivation does not intervene, titanium metal will react violently with the surrounding chemical species (typically, oxygen, water, or other oxidizing species) and will revert to its ionic form.

The second factor that governs the corrosion process of metal biomaterials is kinetic barriers that prevent corrosion not by energetic mechanisms but by physical limitation of the rate at which oxidation or reduction processes can take place. The well known process of passivation, or the formation of a metal-oxide passive film on a metal surface, is an example of a kinetic limitation to corrosion. In general, kinetic barriers to corrosion prevent the migration of metal ions from the metal to the solution, the migration of anions from the solution to the metal, and the migration of electrons across the metal-solution interface. Passive oxide films are the best-known forms of kinetic barriers to corrosion, but there are others, including polymeric coatings.

Most alloys used for orthopaedic appliances rely on the formation of a passive film to prevent oxidation from taking place. These films consist of metal oxides, which form spontaneously on the surface of the metal in such a way that they prevent transport of metal ions and electrons across the film. In order to limit oxidation, passive films must have certain characteristics. They must be non-porous and must fully cover the metal sur-

TABLE
SPECIFICATIONS OF THE AMERICAN SOCIETY FOR TESTING AND MATERIALS

Alloy System	Specification	Fe	C	Cr	Ni	Co	Ti	Al	V
Stainless-steel									
316L	F-138 (grade 2)	Balance	0.03 max.	17-19	13-15.5				
22-13-5	F-1314	Balance	0.03 max.	20.5-23.5	11.5-13.5				0.10-0.30
Cobalt									
Cast	F-75	0.75 max.	0.35 max.	27-30	1.0 max.	Balance			
Forged†	F-799	0.75 max.	0.35 max.	26-30	1.0 max.	Balance			
Wrought	F-90	3.0 max.	0.05-0.15	19-21	9-11	Balance			
Titanium									
Commercially pure	F-67 (grade 4)	0.5 max.	0.1 max.				Balance		
Extra-low interstitial Ti-6Al-4V	F-136	0.25 max.	0.08 max.				Balance	5.5-6.5	3.5-4.5

*Composition is given as the weight per cent.

†The same composition specifications are applicable to the wrought form of this alloy given by specification F-1537.

face; they must have an atomic structure that limits the migration of ions and electrons across the metal oxide-solution interface; and they must be able to remain on the surface of these alloys even with mechanical stressing or abrasion, which can be expected in association with orthopaedic devices. In general terms, the more atomic defects there are in the oxide, the less able the oxide film is to prevent migration of ionic species and the lower the kinetic barrier is to corrosion. These atomic defects include vacancies, which are missing atoms in the oxide crystal, and impurity atoms with different valence states within the oxide crystal. Titanium dioxide is very close to being a stoichiometric oxide; hence, it does not have many ionic defects. This results in an increased resistance to ionic transport. Several treatments have been investigated to determine if the barrier effect of the oxide film can be improved. These treatments include a hot, concentrated nitric-acid bath (American Society for Testing and Materials Specification F86-84), boiling in distilled water¹⁰⁷, and anodization. However, detailed investigations with regard to changes in the structure of the oxide film that are associated with these treatments are incomplete.

Importantly, mechanical factors, such as fretting, micromotion, or applied stresses, may cause the oxide film to abrade or fracture. When an oxide film is ruptured from the metal substrate, unoxidized metal is exposed to solution. Such films tend to reform or repassivate, and the magnitude of the repassivation current densities may be large (for example, as much as one ampere per square centimeter³⁵). This is due to the large driving forces that are present for the oxidation process; when the kinetic barrier is removed, these forces can cause oxidation. However, the extent and duration of the oxidation currents depend on the repassivation kinetics for formation of the oxide film. Hence, the mechanical stability of the oxide film as well as the nature of its repassivation process is central to its performance in orthopaedic applications.

In order to continue corrosion reactions, the electrons that are left behind in the metal must undergo

another reaction (a reduction reaction) to be consumed. A typical reduction reaction in orthopaedic implants is the reduction of oxygen and water to form hydroxide. Reduction reactions can take place either very close to the corresponding oxidation reaction or far from it. An example of the latter is a crevice corrosion reaction, in which the crevice solution becomes relatively depleted in oxygen; thus, while continued oxidation takes place in the crevice, the reduction reaction occurs away from it. In any event, in order for corrosion reactions to progress, there must be a corresponding reduction reaction. If the reduction reaction is eliminated, then corrosion may be suppressed.

Virtually all modern metal orthopaedic implants are fabricated from one of three alloy systems, the composition and the mechanical and physical properties of which conform to the specifications of the American Society for Testing and Materials⁶⁸ (Table II). There is allowable variability in the concentration ranges for the elements used in the alloy, which could potentially lead to subtle differences in mechanical, physical, or electrochemical properties. The potential variability in properties due to slight differences in composition, however, is minor compared with the potential variability introduced by differences in fabrication methodology, heat treatment, cold-working, and surface-finishing. Surface treatments may be particularly important for corrosion and wear properties. Such treatments may involve shot-peening or nitriding and implantation of ions to harden the surface, polishing to remove asperities, and passivation to thicken the protective oxide.

When two dissimilar metals are in contact in an electrolyte solution, there is an electrical potential difference between them (Table I), resulting in a flow of electrons from the more active to the more noble metal. This process is termed galvanic corrosion and results in a corrosive attack on the active metal (anode) and in relative protection of the more noble metal (cathode). Contact between dissimilar metals immersed in an electrolyte may occur commonly in orthopaedic clinical practice. Examples include a stainless-steel cer-

II

FOR THE COMPOSITION OF ALLOYS USED IN ORTHOPAEDIC IMPLANTS^{68*}

Mo	Mn	P	S	Si	N	Cu	Nb	W	O	H
2-3	2.00 max.	0.025 max.	0.01 max.	0.75 max.	0.10 max.	0.50 max.				
2-3	4.0-6.0	0.025 max.	0.010 max.	0.75 max.	0.20-0.40	0.50 max.	0.10-0.30			
5-7	1.0 max.			1.0 max.						
5-7	1.0 max.			1.0 max.	0.25 max.					
	1.0-2.0	0.04 max.	0.03 max.	0.40 max.				14-16		
					0.5 max.				0.4 max.	0.0125 max.
					0.05 max.				0.13 max.	0.012 max.

clage wire in contact with a cobalt or titanium-alloy femoral stem, a cobalt-alloy femoral head in contact with a titanium-alloy femoral stem, and a titanium-alloy screw in contact with a stainless-steel plate. Although it is generally good practice to avoid contact between dissimilar metals, the presence of a passivating oxide film alters the kinetics of the corrosion reaction so that certain combinations of dissimilar metals are not accompanied by accelerated galvanic corrosive attack. Under static conditions in which there is no relative motion (fretting) between the metals, a galvanic couple consisting of cobalt alloy and titanium alloy is stable — that is, there is no accelerated corrosive attack. However, a combination of stainless steel and cobalt alloy or one of stainless steel and titanium alloy is unstable (the steel is more susceptible to attack), and use of either combination should be avoided^{42,59,63,91}.

Galvanic effects also may be created by slight differences in composition (as already discussed) or by differences in metal processing (for example, the use of cast as well as forged cobalt alloy). These more subtle galvanic effects do not seem to result in substantial corrosive attack in the spontaneously passivating metal systems used in orthopaedic applications. Therefore, couples consisting of stainless steel and stainless steel⁸³, cobalt alloy and cobalt alloy⁸¹, and titanium alloy and titanium alloy are considered stable under static conditions. In the presence of fretting, however, the situation may change because the passivating oxide layer may be abraded away, exposing bare metal to the electrolyte solution. In this setting, accelerated corrosion may occur with any combination of metals depending on the nature of the fretting motion, the local solution chemistry, and the microstructure of the metals.

A wide variety of methodologies are used to assess the corrosion properties of orthopaedic alloys. These include immersion-testing, electrochemical tests such as anodic polarization and linear polarization, and other specialized tests such as impedance spectroscopy and stripping analysis. These tests are used to investigate the rate of ion release, the electrochemical conditions that cause oxidation and reduction processes, and the electrical nature of the interface. Other methodologies

allow imaging of the microscopic electrochemical processes occurring at a corroding alloy-solution interface³⁶. There also are several testing methods related to combined mechanical-electrochemical processes such as fretting corrosion, stress corrosion, and corrosion fatigue. These tests typically evaluate how an alloy resists failure in the presence of both processes. A full discussion of these methodologies is beyond the scope of this review and is available elsewhere^{30,46}.

Current Corrosion Processes in Orthopaedics

It is important to understand that the corrosion of orthopaedic biomaterials is not just an exercise in physics and chemistry. There are real problems related to the corrosion of implants that are in current clinical use.

Corrosion at Modular Interfaces of Joint-Replacement Components

A current problem related to orthopaedic alloys is corrosion at the taper connections of modular joint-replacement components. With the large and growing number of total joint designs that include metal-on-metal conical taper connections, the effects of crevices, stress, and motion take on increasing importance. Recent retrieval studies have shown that severe corrosive attack can occur in the crevices formed by these tapers *in vivo* (Fig. 1)^{21,22,34,65}. Gilbert et al. reported that approximately 16 to 35 per cent of 148 retrieved total hip implants showed signs of moderate-to-severe corrosive attack in the head-neck taper connection³⁴. This attack was observed in components consisting of a Ti-6Al-4V-alloy femoral stem and a cobalt-alloy femoral head as well as in those consisting of a cobalt-alloy stem and a cobalt-alloy head. It has been postulated that this corrosion process is the result of a combination of stress and motion at the taper connection and the crevice geometry of the taper³³. The stresses resulting from use of the prosthesis cause fracture and abrasion of the oxide film covering these passive metal surfaces. This in turn causes changes in the metal surface potential, making it more negative, and in the chemistry of the crevice solution as the oxides continuously fracture and repassivate. Such changes may result in deaeration

(loss of oxygen) of the crevice solution and in a decrease of the pH in the crevice^{32,34}, as is expected in crevice corrosive attack. The ultimate result of this process is a loss of the oxide film and its kinetic barrier effect and an increase in the rate of corrosive attack in the taper region.

Severe and extensive corrosive attack has been seen primarily in cobalt-alloy systems with modular taper connections. However, corrosive attack in titanium-alloy stems also has been reported³⁶.

The corrosion processes in cobalt alloy have consisted of intergranular corrosion, etching, selective dissolution of cobalt, and formation of chromium-rich particles including oxides, oxychlorides, and phosphates. The corrosion products generated at the taper connections have migrated into the periprosthetic tissue and the bearing surface of the acetabular component⁹⁴. We know of three instances in which a retrieved cobalt-alloy stem had such extensive intergranular corrosion that fatigue failure had ensued at its neck^{37,54}.

A key factor that may contribute to relative motion (fretting) at modular connections and ultimately to abrasive loss of the passivating oxide layer is angular mismatch between the taper on the male aspect of the connection and the bore on the female aspect. Such a mismatch may result if the tolerances are relatively large, leading to poor mechanical stability of the connection. In this situation, the loads produced during the normal gait cycle may dislodge the interference fit of the modular connection, leading to disruption of the metal surfaces and initiation of the cascade just described³³.

These observations point to the effect of combined

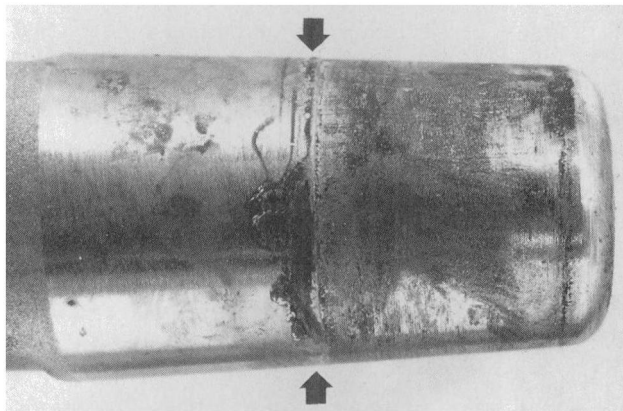


FIG. 1

Photograph of the neck-taper region of a modular prosthesis in which both the head and the stem were made of cobalt alloy. The surface of the neck that had been mated with the head was pitted, etched, and covered with thin films of black corrosion products. In contrast, the area that had been at the opening to the head-neck junction (arrows) had thick, glassy, green deposits of a chromium-phosphate-rich corrosion product ($\times 5$). (Reprinted, with permission, from: Urban, R. M.; Jacobs, J. J.; Tomlinson, M. J.; Gavrilovic, J.; and Andersen, M. E.: Migration of corrosion products from the modular head junction to the polyethylene bearing surface and interface membranes of hip prostheses. In *Total Hip Revision Surgery*, p. 63. Edited by J. O. Galante, A. G. Rosenberg, and J. J. Callaghan. New York, Raven Press, 1995.)

stresses and motion and to the electrochemical processes that occur at metal oxide-solution interfaces. The mechanical integrity of the oxide films that form on these alloys is essential for the long-term stability and survival of the implant.

Internal Fixation Devices

The development of corrosion-resistant, biocompatible metal alloys was one of several essential factors in the evolution of internal fixation as a treatment for closed fractures. The history of this process, until the precursors of modern-day alloys were introduced, was described in detail by Venable and Stuck⁹⁷ and, more recently, by Peltier⁷⁸. Two case reports in which Lane plates were removed after more than fifty years provide additional indication of the corrosion of these devices and the deposition of large amounts of corrosion products in the surrounding tissue^{24,93}. Hundreds of internal fixation devices and early joint-replacement prostheses were examined in retrieval studies in the 1960s and 1970s^{19,20,82,85,86,101,104-106}. Many of the stainless-steel and cobalt-chromium-alloy devices that were used during this period were prone to accelerated corrosion because of improper selection of materials, faulty fabrication techniques, and use of mixed metals. These deficiencies have largely been eliminated in modern implants through sound metallurgical practice and fabrication processes. Although modern, single-part devices used as permanent implants rarely show visible signs of corrosion^{6,8}, Cook et al. found some degree of interface crevice corrosion in 89 per cent of the plates and 88 per cent of the screws of 250 multiple-part stainless-steel internal fixation devices removed between 1977 and 1985²³.

Local Tissue Effects

The tissue surrounding modern implants may include areas of osseointegration and fibrous encapsulation, and there may be a variable foreign-body response to the polyethylene and bone-cement debris produced by joint-replacement devices. Although there is no specific histological evidence of the slow release of metal species that is thought to occur in association with all metal implants, accelerated corrosion and a tissue response that can be related directly to identifiable corrosion products have been demonstrated in the tissue surrounding multiple-part devices^{92,94,105,106}.

Stainless Steel

The work of Williams and Meachim¹⁰⁴, Winter^{105,106}, Sevitt⁸², and French et al.³¹ provides correlated metallurgical and histopathological observations of the local tissue response to the corrosion products of stainless-steel implants used for fixation of long bones. Winter identified these corrosion products with use of electron-microprobe energy-dispersive x-ray analysis and electron diffraction¹⁰⁶. Histological sections of the tissue

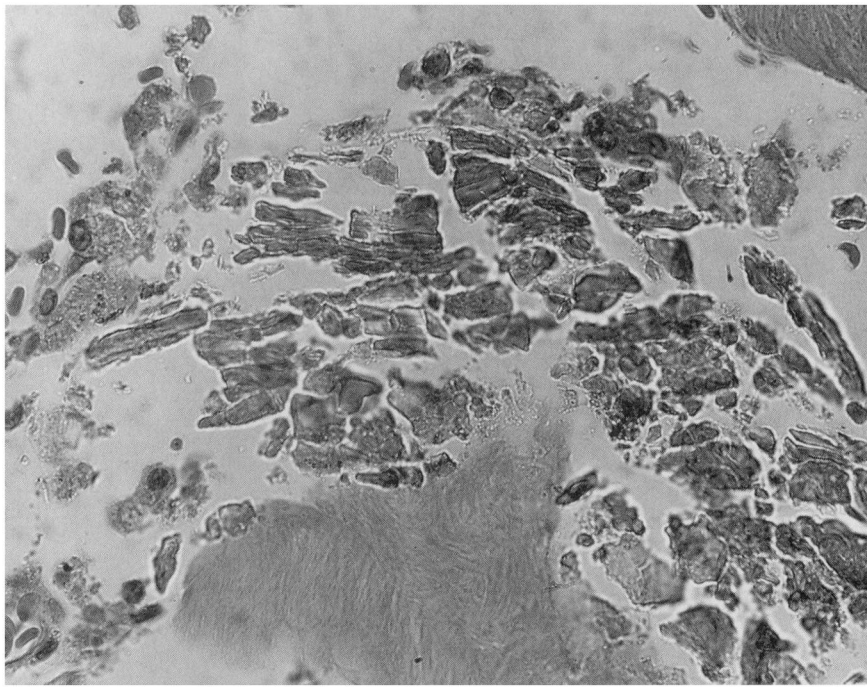


FIG. 2

Histological section, obtained from the cadaver of a patient in whom a fracture of the hip had been treated with internal fixation; the duration of implantation was unknown. The section shows microplates (which appear green), high in chromium, from a fibrous membrane surrounding the corroded stainless-steel screw-plate junction. The largest individual particles were extracellular and measured as much as forty micrometers in their greatest dimension. Smaller particles were contained within macrophages (hematoxylin and eosin, $\times 500$). (Reprinted, with permission, from: Jacobs, J. J.; Gilbert J. L.; and Urban, R. M.: Corrosion of metallic implants. In *Advances in Operative Orthopedics*, edited by R. N. Stauffer. Vol. 2, p. 294. St. Louis, C. V. Mosby, 1994.)

surrounding stainless-steel internal fixation devices generally show encapsulation by a fibrous membrane with little or no inflammation over most of the device⁸⁵. At the screw-plate junctions, however, the membrane often contains macrophages, foreign-body giant cells, and a variable number of lymphocytes in association with two types of corrosion products: iron-containing hemosiderin-like granules, and microplates, which consist of relatively larger particles of a chromium compound (Fig. 2). Microplates have variable morphological characteristics and appear within the tissue as closely packed, plate-like aggregates of particles ranging in size from 0.5 to 5.0 millimeters. They often are found free within acellular collagen or necrotic tissue. Several multinucleated foreign-body giant cells are usually present within or bordering collections of these particles. In hematoxylin-and-eosin preparations, most microplates are yellow or apple-green; however, many stain darkly with hematoxylin, and these microplates also react strongly to stains for iron. Electron-microprobe energy-dispersive x-ray analyses have indicated that microplates are a chromium compound containing iron and a substantial amount of phosphorous¹⁰⁶. The chromium-to-iron ratio of microplates is invariably higher than that of the stainless-steel alloy.

Hemosiderin-like granules often surround collections of microplates, but the granules may be found alone as well. The granules are yellow-brown, mainly spherical, and 0.1 to three micrometers or more in di-

ameter. They are predominantly intracellular and are found most often in macrophages, but they may also be found in fibrocytes. They react strongly for trivalent iron with use of the Prussian-blue reaction, and they closely resemble the hemosiderin pigment from residue of blood in the tissue. X-ray diffraction has indicated¹⁰⁶ that the granules consist of a mixture of at least two iron oxides, $\alpha\text{Fe}_2\text{O}_3$ and $\sigma\text{Fe}_2\text{O}_3$, and the hydrated iron oxides, $\alpha\text{Fe}_2\text{O}_3 \cdot \text{H}_2\text{O}$ and $\sigma\text{Fe}_2\text{O}_3 \cdot \text{H}_2\text{O}$.

Solid products of corrosion also have been reported in association with accelerated corrosion of stainless-steel femoral stems used in hip replacement^{17,75} and with spinal instrumentation⁷³ made of stainless steel. Although these corrosion products may be expected to be similar in composition to those of fracture-fixation plates and screws, they have not been subjected to detailed microchemical analysis, to our knowledge.

Cobalt-Based Alloys

We analyzed the migration of solid corrosion products to the periprosthetic tissue in a study of twenty-five modular cobalt-alloy total hip-replacement femoral components (made by a number of different manufacturers) that had been retrieved at the time of revision or autopsy^{34,96}. The corrosion products were similar regardless of whether the head-neck couple consisted of cobalt alloy and cobalt alloy, cobalt alloy and titanium alloy, or cobalt alloy and alumina ceramic. The principal corrosion product was identified, with use of electron-

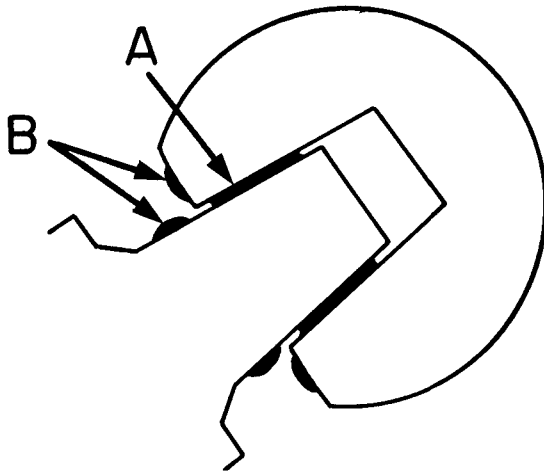


FIG. 3

Schematic drawing showing the locations of corrosion products from a corroded modular hip prosthesis. A = thin interfacial layer of mixed oxides and chlorides within the crevice formed by the junction of the head and the neck taper, and B = thicker deposits of chromium-orthophosphate hydrate-rich corrosion products around the opening of the crevice. (Reprinted, with permission, from: Urban, R. M.; Jacobs, J. J.; Gilbert, J. L.; Rice, S. B.; Jasty, M.; Bragdon, C. R.; and Galante, J. O.: Characterization of solid products of corrosion generated by modular-head femoral stems of different designs and materials. In *Modularity of Orthopedic Implants*, edited by D. E. Marlowe, J. E. Parr, and M. B. Mayor. American Society for Testing and Materials Special Technical Publication 1301, p. 36. West Conshohocken, Pennsylvania, American Society for Testing and Materials, 1997.)

microprobe energy-dispersive x-ray analysis as well as Fourier-transform infrared microprobe spectroscopy, as a chromium-orthophosphate hydrate-rich material. This corrosion product was present at the modular head-neck

junction (Fig. 3) and as particles within the joint pseudocapsules, within the bone-implant interface membranes, and at sites of femoral osteolytic lesions^{54,94,96}. *In vitro* studies of the cellular response to particles fabricated from commercial preparations of chromium phosphate demonstrated that the material is a potent macrophage-monocyte activator and has the capacity to stimulate bone resorption in organ culture in a dose-dependent manner⁶¹.

In several instances, particles of the chromium-orthophosphate hydrate-rich material were found at the bearing surface of the polyethylene acetabular liners, suggesting their participation in three-body wear and an increased production of polyethylene debris⁹⁴. Particles of the corrosion product found in the tissue ranged in size from submicrometer to aggregates as large as 500 micrometers. On visualization with light microscopy, the particles were similar in appearance to the chromium-containing microplates observed in association with corroded stainless-steel implants. They were plate-like, pale yellow or green, translucent, and usually unstained in hematoxylin-and-eosin preparations (Fig. 4). The larger particles were free within areas of marked fibrosis or necrosis or were associated with foreign-body giant cells. Most particles were less than five micrometers in size and were found within macrophages. In stained sections, these small particles imparted a granular appearance to the cells that contained them. The particles were not birefringent in polarized light. On scanning-electron-microscope backscattered-electron images of unstained sections, the particles were demonstrated by

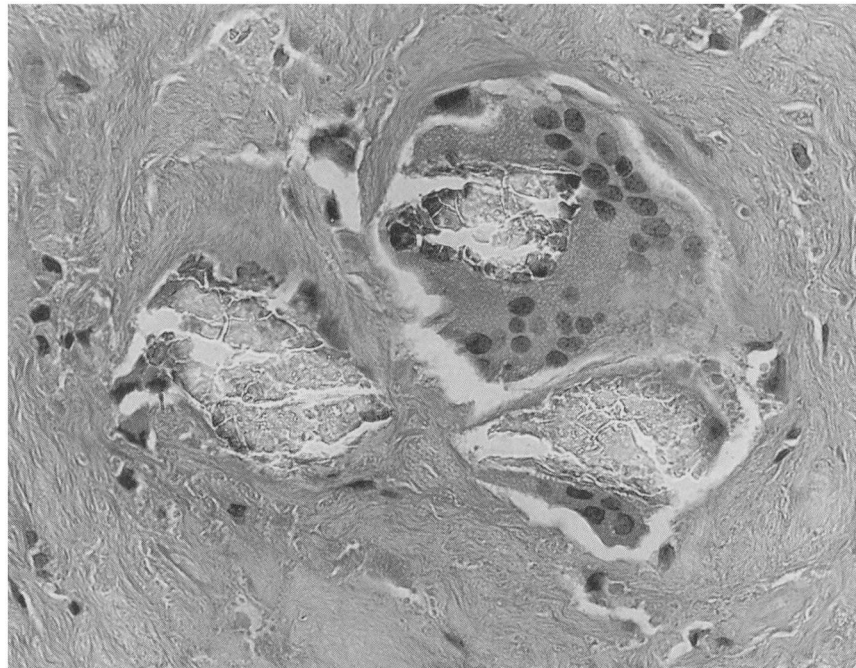


FIG. 4

Photomicrograph showing foreign-body giant cells surrounding several fifty to seventy-micrometer-thick chromium-orthophosphate hydrate-rich particles in an area of marked fibrosis in the joint pseudocapsule adjacent to a corroded modular hip prosthesis (hematoxylin and eosin, $\times 500$).

their bright appearance because of the relatively high atomic number of chromium.

Mathiesen et al. reported extensive necrosis of peri-prosthetic tissue due to metal toxicity in association with four of nine cobalt-chromium-alloy Lord hip prostheses that had been inserted without cement and had been retrieved at revision⁶⁵. All four implants had bone and soft-tissue discoloration as well as black deposits of corrosion products at the modular head-neck junction. The corrosion deposits were visible on radiographs that had been made before the revision of one implant; they appeared as a radiopaque shadow at the superior angle between the head and neck. Histological sections of the tissue surrounding the corroded prostheses showed extensive necrosis and various degrees of histiocytic and foreign-body giant-cell proliferation as well as infiltration of lymphocytes and plasmacytes. Vascular inflammation was present in association with two of the implants⁶⁵. Svensson et al. reported in detail on one of these patients, who had an extensive soft-tissue reaction that clinically mimicked a sarcoma⁹². The patient had a history of possible allergic skin reactions and, after the revision, had a positive cutaneous reaction to cobalt and chromium solutions on dermal tests. No neoplastic cells were found in the specimens that had been obtained at revision. Histopathologically, there was extensive necrosis, fibrosis, and inflammation. The inflammation was dominated by lymphocytes, macrophages, and a substantial number of eosinophils. Several small vessels demonstrated obliterative, necrotizing arteritis. Epithelioid granulomas and giant cells containing metal particles also were observed. These findings suggested a hypersensitivity reaction, partly of the cell-mediated type, leading to a chronic granulomatous inflammation and vasculitis that probably were triggered by local release of metal ions from the corroding modular junction⁹².

We reported an unusual foreign-body reaction to particulate products of corrosion and wear in the tissue around a failed total knee implant that had been inserted without cement and that was composed of several different cobalt alloys⁵¹. The patient had a tumorlike mass in the right knee in association with ipsilateral inguinal adenopathy. Radiographs revealed a failed metal-backed patellar component, free metal debris, and osteolysis adjacent to fixation screws in the proximal aspect of the tibia. The histological appearance of lymph nodes and the tumor was that of sarcoid-like non-caseating granulomas associated with extensive cobalt-alloy debris⁵¹.

Titanium-Based Alloys

The degradation products that have been observed in histological sections of tissue adjacent to titanium-based alloys generally have been of a different nature than the precipitates associated with stainless-steel and cobalt-based alloys that have undergone accelerated corrosion.

Despite the remarkable resistance of titanium-based alloys to corrosion, there have been several reports of discoloration due to metal debris in the periprosthetic tissue. Agins et al. reported a marked histiocytic, lymphoplasmacytic, and foreign-body giant-cell reaction to abundant metal, polyethylene, and bone-cement debris in the tissue around nine titanium-alloy stems that had been revised because of aseptic loosening or infection¹. Focal necrosis was seen in all of the hips. Atomic absorption spectrophotometry, performed on samples of the tissue removed from paraffin-tissue blocks, revealed that the ratios of titanium, aluminum, and vanadium were similar to those in the alloy, suggesting that the metal debris represented wear particles from the head or stem rather than precipitated dissolution products¹.

Black et al. reported the clinical failure of a total hip-replacement prosthesis made of Ti-6Al-4V alloy and ultra-high molecular weight polyethylene¹¹. Both components had been fixed with bone cement. The failure was due to excessive wear of the titanium-alloy femoral head in the absence of loosening of either component. In contrast to the findings of Agins et al.¹, the tissue response in the joint pseudocapsule of this patient was characterized by fine metal debris within histiocytes in the absence of lymphoplasmacytic leukocytes, foreign-body giant cells, or necrosis. Electron-microprobe analysis of the metal particles demonstrated titanium, aluminum, and vanadium in proportion to their concentrations in Ti-6Al-4V alloy¹¹.

Meachim and Williams studied nineteen commercially pure titanium, non-articulating implants (seventeen pin-and-plate devices and two Harrington rods) and the surrounding tissue⁶⁷. The specimens were examined with histological and metallurgical techniques, and the titanium content of the tissue adjacent to the implant was estimated with neutron-activation analysis. Variable amounts of titanium particles within macrophages and fibrocytes were found within densely collagenous membranes that were adjacent to the implant. Foreign-body giant cells were rare. No specimen had metallurgical evidence of corrosion other than areas that appeared duller than others on gross examination. No obvious relationship was found between the titanium content of the tissue and the presence of inflammatory cells, the presence of granulation tissue, or the amount of necrotic debris at the tissue-implant interface⁶⁷.

Willert et al. reported the unique observation of crevice corrosion in association with twenty-eight Müller straight-stem femoral components, made of Ti-6Al-4V or Ti-Al-Nb alloy, that had been implanted with bone cement during total hip replacements¹⁰². The retrieved components had been *in situ* for a mean of twenty-six months. Pain was the primary reason for revision. Corrosion products in the form of violet or black deposits and white deposits, described as titanium oxides and hydroxides, were found at the interface

between the stem and the surrounding bone cement, particularly at the distal aspect of the stem. Particles of the corrosion products in the periprosthetic tissue appeared as highly birefringent, translucent, rounded grains and rectangular plaques. The smaller of these particles, found within macrophages and giant cells (often together with contrast-medium material from the cement), occasionally formed cellular granulomas¹⁰².

More typically, the particles observed in local tissue surrounding titanium-alloy implants appear to be wear products with the same elemental composition as the parent alloy¹¹¹ rather than precipitated corrosion products, as has been demonstrated in association with stainless-steel and cobalt-alloy components. However, this fine wear debris presents an enormous surface area for electrochemical dissolution, which, in all likelihood, is a major factor contributing to the local cellular response as well as the systemic increases in titanium that have been measured^{26,49}.

Remote and Systemic Effects

General Considerations

There is a long clinical experience with permanent and temporary metal implants^{78,97}. The biocompatibility of such implants with regard to the local tissue reaction has always been a concern. The implant, or wear debris generated from it, may release chemically active metal ions into the tissue. Although these ions may stay bound to local tissue, there is an increasing recognition that they may also bind to protein moieties that are transported in the bloodstream and lymphatics and, hence, to remote organs¹¹⁰. There are four basic issues associated with metal-ion release: the amount of metal released from the implant, the site to which the metal is transported and the quantity that is transported, the chemical form of the released metal (for example, inorganic precipitate or soluble organometallic complex), and the pathophysiological consequences of such metal release. There is an increasing body of literature addressing the first two questions as they relate to total joint replacement; however, little is currently known about the latter two areas.

The concern about the release and distribution of metal degradation products is justified by the known potential toxicities of titanium, aluminum, vanadium, cobalt, chromium, and nickel (the elements used in modern orthopaedic alloys)^{6,100}. The toxicology of these elements has been described in several review articles^{27,40,56,60,88,103}. In general terms, metal toxicity can present as metabolic alterations, alterations in host-parasite interactions, immunological sensitization by metal hapten moieties (specific immunological activation), non-specific immunological suppression due to antiche-motactic properties^{13,70}, and chemical carcinogenesis^{84,89}. However, when the litany of documented toxicities of these elements is considered, it should be emphasized that they generally apply to soluble forms of the ele-

ments and may not apply to the degradation products of prosthetic implants.

The carcinogenic potential of the metal elements used in total hip-arthroplasty components is a concern, particularly because the high surface area of porous-coated devices inserted without cement is intended for implants used in younger, more active patients who may have a postoperative life expectancy of more than thirty years. The carcinogenic potential of these implant materials has been documented in animal studies^{44,62,84}. For example, Memoli et al. reported a small increase in the prevalence of sarcoma in rats that had an implant with a high cobalt, chromium, or nickel content⁶⁹. Lymphomata with osseous involvement were also more common in rats with a metal implant⁶⁹. Bouchard et al., also in a study of rats, noted tumors adjacent to the sites of both cobalt and titanium-based-alloy implants¹². The tumors were associated with loosening of the implant, suggesting that a foreign-body reaction was the primary mechanism of carcinogenesis¹².

There have been a number of reports of tumors at the sites of implants in dogs and cats; most of these lesions have been osteosarcomas or fibrosarcomas associated with stainless-steel internal fixation devices⁷. There have been relatively few reports of malignant tumors associated with total joint replacements in humans⁴⁸, but the number of case reports is increasing. Concerted efforts are currently under way to accumulate cases of malignant neoplasms associated with total joint replacements, in order to better define the risks prospectively^{2,41}.

There have been even fewer large-scale epidemiological studies of the carcinogenic potential of metal implants. One such investigation documented an increased prevalence of leukemia and lymphomata in patients who had a cobalt-alloy total hip replacement³⁸. Other studies have supported this finding in patients who had a metal-on-metal device^{98,99}. Recent studies failed to confirm an increased prevalence of leukemia and lymphomata; however, they did not include as large a proportion of subjects who had a metal-on-metal device^{39,64,74}. Interestingly, they also demonstrated a decreased prevalence of other site-specific malignant tumors, including those of the lung^{64,99}, breast³⁸, and stomach^{74,99}.

At this point in time, the association between release of metal from orthopaedic implants and any metabolic, bacteriological, immunological, or carcinogenic toxicity is conjectural. Cause and effect have not been established in human subjects, in large part because most diseases that could result from systemic and remote metal toxicity can be expected to occur at a finite frequency in any population of orthopaedic patients. Thus, the identification of disease processes related to but at a site remote from an implant depends either on the availability of comparative epidemiological data or on the ability to perform tests on the patient before and after removal of the device. Currently, there is a dearth

of such data with regard to any remote or systemic effects in patients who have had a joint-replacement procedure.

Studies of Total Joint Replacement in Humans

The presence of metal degradation products generated by corrosion and wear has been documented locally^{1,25,71} and systemically^{4,9,25,58,71,76,77,90} in animal models^{28,29,108-110} and in humans^{1,5,9-11,14,25,26,47,49-55,58,71,72,76,77,87,90}. Earlier studies were hampered by methodological problems, particularly contamination, involved with the measurement of concentrations of metal in the parts-per-billion range⁷². More precise data have emerged as methodology and instrumentation have evolved.

Sunderman et al. reported increased levels of cobalt in the serum and urine six to 120 weeks after total knee replacement, and they noted substantially increased levels in two patients who had a loose prosthesis⁹⁰. One of these two patients also had an increased level of chromium in the serum and urine, and transient increases in the levels of nickel in the urine and serum were noted immediately postoperatively. Those authors concluded that there was no sign of metal toxicity in any of their patients, and all levels that were measured were within limits considered acceptable for occupational exposure⁹⁰.

Michel et al., in a prospective study of ten patients who had had a total knee arthroplasty with use of cobalt-based-alloy components, found a twofold increase in the level of cobalt in the serum and whole blood ninety days after the operation⁷². In a companion retrospective study, four of twenty-three patients who had had a total hip or total knee replacement with use of cobalt-based-alloy components had levels of cobalt in the serum of more than two parts per billion (highest level, fifty parts per billion) less than one to 152 months postoperatively; the controls in that study had levels of 0.33 part per billion⁷². None of the devices was reported to be loose, and no increase in the level of chromium in the serum was documented⁷².

We performed several studies to investigate metal-ion release after total joint replacement with use of titanium-based-alloy components. In a retrospective study, the concentration of titanium in the serum of twenty-one patients who had a loose titanium-containing total hip-replacement component was increased approximately twofold compared with the level in twenty-one controls⁴⁹. No significant differences were detected in the concentration of titanium or aluminum in the urine or in the concentration of aluminum in the serum between these two groups or between either of them and a group of twenty-one patients who had a stable implant. The concentration of vanadium was uniformly low in all three groups⁴⁹.

We also conducted a retrospective study of the serum concentration and urinary excretion of metal in thirty-six patients who had total knee-replacement

components containing titanium-based alloy and in twenty-one controls who did not have an implant⁵². The patients who had wear couples consisting of carbon-fiber-reinforced polyethylene and titanium-based alloy had a tenfold increase in the concentration of titanium in the serum compared with the controls at a mean of four years after implantation. Equally dramatic, although somewhat more predictable, were the increases noted in patients who had a failed metal-backed patellar component in which unintended metal-on-metal articulation was occurring. These individuals had the highest levels of titanium in the serum (mean, 114 parts per billion; range, fifteen to 285 parts per billion) — as much as two orders of magnitude higher than the values for the controls. Increases in the level of titanium in the urine, with values as high as 6.6 parts per billion, also were noted in this group. Interestingly, there was no increase in the level of aluminum in the serum or urine in any group that was studied. The levels of vanadium in the serum and urine were too low to allow meaningful comparisons.

Stulberg et al. reported substantial increases in the levels of titanium and aluminum as well as slight increases in the levels of vanadium, cobalt, and chromium in the serum of patients who had a failed patellar component⁸⁷.

Because of the inherent variability in metal-ion content between normal individuals (that is, those who do not have an implant)⁷² and in the same individual at different times, we performed a prospective, controlled, longitudinal study in which the level of metal in the serum of seventy-five patients was measured both before the operation and at regular intervals thereafter⁴⁷. With use of this study design, each patient serves as his or her own control. Patients who had a well functioning primary total hip replacement with titanium-containing components had as much as a threefold increase in the concentration of titanium thirty-six months postoperatively, whereas those who had a well functioning prosthesis with cobalt-alloy components had increases in the levels of chromium in the serum and urine of as much as fivefold and eightfold, respectively. The predominant source of disseminated chromium-degradation products was probably the modular head-neck junction; passive dissolution of extensively porous-coated cobalt-alloy stems was not a dominant mode of metal release⁴⁷.

We also prospectively studied fifteen patients who had a total knee replacement, without cement, that included a conventional polyethylene articular surface and a nitrogen ion-implanted titanium-alloy counterface⁵⁰. Samples of serum, obtained for a maximum of sixty months postoperatively, revealed a twofold-to-fivefold increase in the level of titanium, at all of the intervals that were studied. All of the patients had an excellent clinical result and no evident radiographic complications.

Because of the findings of mechanically assisted

crevice corrosion in patients who have had a total hip arthroplasty with use of a modular femoral stem^{21,22,34,65}, we undertook a retrospective study to examine the levels of cobalt, chromium, and nickel in the serum and urine of patients in whom a modular implant had failed⁵⁴. We found increases in the levels of cobalt in the serum and chromium in the urine of ten patients who had moderate-to-severe corrosion at the modular junction compared with ten controls and five patients who had no or mild corrosion⁵⁴.

The highest levels of cobalt and chromium in the serum and of chromium in the urine were observed in individuals who had a total hip system incorporating metal-on-metal bearing couples⁵³. We found a ninefold increase in the level of chromium in the serum, a thirty-fivefold increase in the level of chromium in the urine, and at least a threefold increase in the level of cobalt in the serum of eight patients in whom a McKee-Farrar total hip implant had been clinically successful for more than twenty years. Even higher increases were seen in six patients who had had a metal-on-metal surface-replacement prosthesis for less than two years.

Autopsy Studies

Michel et al. reported on two postmortem specimens with cobalt-based-alloy total joint-replacement components⁷². One specimen showed substantial increases in the concentration of cobalt in the heart, liver, and spleen, and the other showed an increased level of cobalt in the lymphatic tissue and the heart. In addition, one specimen had an increased level of chromium in the aorta, heart, liver, pancreas, and spleen⁷². Dobbs and Minski also reported increased concentrations of cobalt and chromium in remote tissue (lung, kidney, liver, and spleen) in a cadaver that had bilateral cobalt-based-alloy total hip components²⁵.

Case et al. reported the results of a study of thirteen cadavera that had an orthopaedic implant¹⁸. Five had stainless-steel dynamic hip screws; four, a stainless-steel total hip replacement; three, a cobalt-alloy hemiprosthesis; and one, a stainless-steel and titanium-alloy total knee replacement. (The study included an additional seven cadavera that did not have an implant.) Metal originating from the implant was found in the local and distant lymph nodes and in the spleen, liver, and bone marrow with use of light and electron microscopy and inductively coupled plasma-mass spectrometry. The levels of metal were highest in the cadavera that had a loose, worn implant¹⁸.

We studied the levels of metal in remote as well as periprosthetic tissue in eight cadavera that had a total hip replacement with titanium-alloy components⁵⁵. We compared the levels in the remote tissue with those measured in five control cadavera that did not have a metal implant. Initially, we focused on the levels of metal within the reticuloendothelial organs (the liver, spleen, and lung). In the control specimens, the levels

of titanium, aluminum, and vanadium in the joint capsule and spleen were generally lower than the limit for detection of these elements, whereas the concentrations of metal in the liver and lung tissue usually were detectable and were quite variable. The cadavera that had an implant had increased levels of titanium, aluminum, and vanadium in the joint pseudocapsule. Importantly, the levels of titanium in the spleen were significantly increased compared with those for the controls ($p < 0.01$). Selected specimens also had increased concentrations of titanium in the liver. The levels of metal in the lung were highly variable in the cadavera that did and did not have an implant.

We recently performed a postmortem examination of a subject who had been enrolled in a prospective study of metal-ion release in association with primary total hip replacement⁴⁷, so both longitudinal concentrations of metal in the serum as well as concentrations in remote tissue could be measured. Markedly increased levels of titanium, aluminum, and vanadium were found in the periprosthetic (local) tissue; increased levels of titanium also were found in the spleen. However, the concentrations of titanium and aluminum in the serum had not increased over the three-year study period. Thus, even in the absence of an increase in the level of metal in the serum, deposition of metal can occur locally and in remote organ stores in association with a well functioning device⁵⁵.

Our autopsy studies have revealed that metal particles from joint-replacement components may migrate to the liver and spleen and that particulate corrosion products from these implants may migrate to regional and para-aortic lymph nodes^{55,95}. The presence of these disseminated particles was associated with multiple implants, revision of loose implants, and primary arthroplasty components that had been *in situ* for a long duration⁹⁵. Although neither our series nor that of Case et al.¹⁸ demonstrated toxic consequences from these systemically disseminated particles, a recent report documented symptomatic, granulomatous hepatitis in association with extensive deposition of titanium-alloy particles in a patient who had a failed total hip replacement^{45,79}.

Future Directions

Corrosion of orthopaedic implants remains a serious clinical concern. Even though the freely corroding implant materials used in the past have been replaced with modern corrosion-resistant superalloys, deleterious corrosion processes have been observed in certain clinical settings. There is reason to believe that attention to variables related to metallurgical processing, tolerances of modular connections, surface-processing modalities, and appropriate selection of materials can decrease the rate of corrosion and minimize the potential for adverse clinical outcomes. For example, a recent study by Maurer et al. showed that nitriding can reduce the magnitude of fretting corrosion of Ti-6Al-4V devices⁶⁶.

Similarly, Buchanan et al. found that implantation of ions can improve the resistance to wear-accelerated corrosion phenomena^{15,16}. The mechanical-electrochemical interactions of passive metal-oxide surfaces must be investigated further. The stresses and motion that are needed to fracture passivating oxide films, as well as the effects of repeated oxide abrasion on the electrochemical behavior of the interface and ultimately the implant, are areas of active investigation.

The role of particulate corrosion products in adverse local tissue reactions also needs to be investigated further. The initial studies described in this paper suggest that particulate corrosion products may play an important role in periprosthetic bone loss. These associations must be defined further with use of both clinical retrieval studies and *in vitro* cell-culture experiments.

Finally, the clinical ramifications of increases in metal content in body fluids and remote organs of patients who

have a metal implant need to be elucidated. Considerable work is required to discern the chemical form of the metal, the nature of its ligands, and ultimately the potential toxicity.

Metal implants for use in both permanent joint-replacement components and internal fixation devices are crucial tools in the armamentarium of the orthopaedic surgeon who treats traumatic, neoplastic, and degenerative disorders of the musculoskeletal system. For the most part, the application of these metal implants has been quite successful, with few serious short and long-term clinical sequelae. However, as we gain more experience with these devices, it is evident that, in certain situations, electrochemical degradative processes may compromise the clinical outcome and lead to adverse local and systemic effects. A continued awareness of these issues is needed within the orthopaedic community.

References

1. Agins, H. J.; Alcock, N. W.; Bansal, M.; Salvati, E. A.; Wilson, P. D., Jr.; Pellicci, P. M.; and Bullough, P. G.: Metallic wear in failed titanium-alloy total hip replacements. A histological and quantitative analysis. *J. Bone and Joint Surg.*, 70-A: 347-356, March 1988.
2. Apley, A. G.: Malignancy and joint replacement: the tip of an iceberg? [editorial]. *J. Bone and Joint Surg.*, 71-B(1): 1, 1989.
3. Bard, A. J., and Faulkner, L. R.: *Electrochemical Methods: Fundamentals and Applications*. New York, Wiley, 1980.
4. Bartolozzi, A., and Black, J.: Chromium concentrations in serum, blood clot and urine from patients following total hip arthroplasty. *Biomaterials*, 6: 2-8, 1985.
5. Betts, F.; Wright, T.; Salvati, E. A.; Boskey, A.; and Bansal, M.: Cobalt-alloy metal debris in periarticular tissues from total hip revision arthroplasties. Metal contents and associated histologic findings. *Clin. Orthop.*, 276: 75-82, 1992.
6. Black, J.: Does corrosion matter? [editorial]. *J. Bone and Joint Surg.*, 70-B(4): 517-520, 1988.
7. Black, J.: *Orthopedic Biomaterials in Research and Practice*, pp. 292-295. New York, Churchill Livingstone, 1988.
8. Black, J.: *Biological Performance of Materials: Fundamentals of Biocompatibility*, pp. 55-56. New York, Marcel Dekker, 1992.
9. Black, J.; Maitin, E. C.; Gelman, H.; and Morris, D. M.: Serum concentrations of chromium, cobalt and nickel after total hip replacement: a six month study. *Biomaterials*, 4: 160-164, 1983.
10. Black, J.; Skipor, A.; Jacobs, J.; Urban, R. M.; and Galante, J. O.: Release of metal ions from titanium-base alloy total hip replacement prostheses. *Trans. Orthop. Res. Soc.*, 14: 501, 1989.
11. Black, J.; Sherk, H.; Bonini, J.; Rostoker, W. R.; Schajowicz, F.; and Galante, J. O.: Metallosis associated with a stable titanium-alloy femoral component in total hip replacement. A case report. *J. Bone and Joint Surg.*, 72-A: 126-130, Jan. 1990.
12. Bouchard, P. R.; Black, J.; Albrecht, B. A.; Kaderly, R. E.; Galante, J. O.; and Pauli, B. U.: Carcinogenicity of CoCrMo (F-75) implants in the rat. *J. Biomed. Mater. Res.*, 32: 37-44, 1996.
13. Bravo, I.; Carvalho, G. S.; Barbosa, M. A.; and de Sousa, M.: Differential effects of eight metal ions on lymphocyte differentiation antigens *in vitro*. *J. Biomed. Mater. Res.*, 24: 1059-1068, 1990.
14. Brien, W. W.; Salvati, E. A.; Betts, F.; Bullough, P.; Wright, T.; Rinnac, C.; Buly, R.; and Garvin, K.: Metal levels in cemented total hip arthroplasty. A comparison of well-fixed and loose implants. *Clin. Orthop.*, 276: 66-74, 1992.
15. Buchanan, R. A.; Rigney, E. D., Jr.; and Williams, J. M.: Ion implantation of surgical Ti-6Al-4V for improved resistance to wear-accelerated corrosion. *J. Biomed. Mater. Res.*, 21: 355-366, 1987.
16. Buchanan, R. A.; Rigney, E. D., Jr.; and Williams, J. M.: Wear-accelerated corrosion of Ti-6Al-4V and nitrogen-ion-implanted Ti-6Al-4V: mechanisms and influence of fixed-stress magnitude. *J. Biomed. Mater. Res.*, 21: 367-377, 1987.
17. Burleigh, T. D.; Shanbhag, A. S.; Birch, J. M.; Musolino, M. C.; and Pettit, F. S.: Corrosion in stainless steel hip prostheses: a study of two implants retrieved after a long service life [abstract]. *Trans. Soc. Biomater.*, 18: 330, 1995.
18. Case, C. P.; Langkamer, V. G.; James, C.; Palmer, M. R.; Kemp, A. J.; Heap, P. F.; and Solomon, L.: Widespread dissemination of metal debris from implants. *J. Bone and Joint Surg.*, 76-B(5): 701-712, 1994.
19. Cohen, J., and Wulff, J.: Clinical failure caused by corrosion of a vitallium plate. Case report, new testing methods for crevice corrosion, and new techniques for fashioning cobalt chromium alloys to be used in surgical implants. *J. Bone and Joint Surg.*, 54-A: 617-628, April 1972.
20. Colangelo, V. J., and Greene, N. D.: Corrosion and fracture of type 316 SMO orthopedic implants. *J. Biomed. Mater. Res.*, 3: 247-265, 1969.
21. Collier, J. P.; Surprenant, V. A.; Jensen, R. E.; and Mayor, M. B.: Corrosion at the interface of cobalt-alloy heads on titanium-alloy stems. *Clin. Orthop.*, 271: 305-312, 1991.
22. Collier, J. P.; Surprenant, V. A.; Jensen, R. E.; Mayor, M. B.; and Surprenant, H. P.: Corrosion between the components of modular femoral hip prostheses. *J. Bone and Joint Surg.*, 74-B(4): 511-517, 1992.
23. Cook, S. D.; Thomas, K. A.; Harding, A. F.; Collins, C. L.; Haddad, R. J., Jr.; Milicic, M.; and Fischer, W. L.: The *in vivo* performance of 250 internal fixation devices: a follow-up study. *Biomaterials*, 8: 177-184, 1987.
24. Danzig, L. A.; Woo, S. L-Y.; Akeson, W. H.; Jemmott, G. F.; and Wickham, M. G.: Internal fixation plates after fifty-six years of implantation: report of a case. *Clin. Orthop.*, 149: 201-206, 1980.

25. **Dobbs, H. S., and Minski, M. J.:** Metal ion release after total hip replacement. *Biomaterials*, 1: 193-198, 1980.
26. **Dorr, L. D.; Bloebaum, R.; Emmanual, J.; and Meldrum, R.:** Histologic, biochemical, and ion analysis of tissue and fluids retrieved during total hip arthroplasty. *Clin. Orthop.*, 261: 82-95, 1990.
27. **Elinder, C. G., and Friberg, L.:** Cobalt. In *Handbook of the Toxicology of Metals*, edited by L. Friberg, G. F. Nordberg, and V. B. Vouk. Ed. 2, vol. 2, pp. 211-232. Amsterdam, Elsevier, 1986.
28. **Ferguson, A. B., Jr.; Laing, P. G.; and Hodge, E. S.:** The ionization of metal implants in living tissues. *J. Bone and Joint Surg.*, 42-A: 77-90, Jan. 1960.
29. **Ferguson, A. B., Jr.; Akahoshi, Y.; Laing, P. G.; and Hodge, E. S.:** Characteristics of trace ions released from embedded metal implants in the rabbit. *J. Bone and Joint Surg.*, 44-A: 323-336, March 1962.
30. **Fontana, M. G., and Greene, N. D.:** *Corrosion Engineering*. New York, McGraw-Hill, 1978.
31. **French, H. G.; Cook, S. D.; and Haddad, R. J., Jr.:** Correlation of tissue reaction to corrosion in osteosynthetic devices. *J. Biomed. Mater. Res.*, 18: 817-828, 1984.
32. **Gilbert, J. L., and Buckley, C. A.:** Mechanical-electrochemical interactions during in vitro fretting corrosion tests of modular taper connections. In *Total Hip Revision Surgery*, pp. 41-50. Edited by J. O. Galante, A. G. Rosenberg, and J. J. Callaghan. New York, Raven Press, 1995.
33. **Gilbert, J. L., and Jacobs, J. J.:** The mechanical and electrochemical processes associated with taper fretting crevice corrosion: a review. In *Modularity of Orthopedic Implants*, edited by D. E. Marlowe, J. E. Parr, and M. B. Mayor. American Society for Testing and Materials Special Technical Publication 1301, pp. 45-59. West Conshohocken, Pennsylvania, American Society for Testing and Materials, 1997.
34. **Gilbert, J. L.; Buckley, C. A.; and Jacobs, J. J.:** In vivo corrosion of modular hip prosthesis components in mixed and similar metal combinations. The effect of crevice, stress, motion and alloy coupling. *J. Biomed. Mater. Res.*, 27: 1533-1544, 1993.
35. **Gilbert, J. L.; Buckley, C. A.; and Lautenschlager, E. P.:** Titanium oxide film fracture and repassivation: the effect of potential, PH and aeration. In *Medical Applications of Titanium and Its Alloys; the Material and Biological Issues*, edited by S. A. Brown and J. E. Lemons. American Society for Testing and Materials Special Technical Publication 1272, pp. 199-215. West Conshohocken, Pennsylvania, American Society for Testing and Materials, 1996.
36. **Gilbert, J. L.; Smith, S. M.; and Lautenschlager, E. P.:** Scanning electrochemical microscopy of metallic biomaterials: reaction rate and ion release imaging modes. *J. Biomed. Mater. Res.*, 27: 1357-1366, 1993.
37. **Gilbert, J. L.; Buckley, C. A.; Jacobs, J. J.; Bertin, K. C.; and Zernich, M. R.:** Intergranular corrosion-fatigue failure of cobalt-alloy femoral stems. A failure analysis of two implants. *J. Bone and Joint Surg.*, 76-A: 110-115, Jan. 1994.
38. **Gillespie, W. J.; Frampton, C. M. A.; Henderson, R. J.; and Ryan, P. M.:** The incidence of cancer following total hip replacement. *J. Bone and Joint Surg.*, 70-B(4): 539-542, 1988.
39. **Gillespie, W. J.; Henry, D. A.; O'Connell, D. L.; Kendrick, S.; Juszcak, E.; McInnery, K.; and Derby, L.:** Development of hematopoietic cancers after implantation of total joint replacement. *Clin. Orthop.*, 329S: S290-S296, 1996.
40. **Gitelman, H. J.:** *Aluminum and Health: A Critical Review*. New York, Marcel Dekker, 1989.
41. **Goodfellow, J.:** Malignancy and joint replacement [editorial]. *J. Bone and Joint Surg.*, 74-B(5): 645, 1992.
42. **Griffin, C. D.; Buchanan, R. A.; and Lemons, J. E.:** In vitro electrochemical corrosion study of coupled surgical implant materials. *J. Biomed. Mater. Res.*, 17: 489-500, 1983.
43. **Handbook of Chemistry and Physics**, pp. D133-D135. Boca Raton, Florida, CRC Press, 1982.
44. **Hueper, W. C.:** Experimental studies in metal carcinogenesis. I. Nickel cancers in rats. *Texas Rep. Biol. and Med.*, 10: 167-186, 1952.
45. **Jacobs, J. J., and Urban, R. M.:** More on reaction to a foreign body after hip replacement [letter]. *New England J. Med.*, 335: 1690-1691, 1996.
46. **Jacobs, J. J.; Gilbert, J. L.; and Urban, R. M.:** Corrosion of metallic implants. In *Advances in Operative Orthopedics*, edited by R. N. Stauffer. Vol. 2, pp. 279-319. St. Louis, C. V. Mosby, 1994.
47. **Jacobs, J. J.; Skipor, A. K.; and Patterson, L. M.:** A prospective, controlled study of metal release in patients undergoing primary total hip replacement. Unpublished data.
48. **Jacobs, J. J.; Rosenbaum, D. H.; Hay, R. M.; Gitelis, S.; and Black, J.:** Early sarcomatous degeneration near a cementless hip replacement. A case report and review. *J. Bone and Joint Surg.*, 74-B(5): 740-744, 1992.
49. **Jacobs, J. J.; Skipor, A. K.; Black, J.; Urban, R. M.; and Galante, J. O.:** Release and excretion of metal in patients who have a total hip-replacement component made of titanium-base alloy. *J. Bone and Joint Surg.*, 73-A: 1475-1486, Dec. 1991.
50. **Jacobs, J. J.; Skipor, A. K.; Patterson, L. M.; Black, J.; and Galante, J. O.:** Serum titanium concentration in patients with cementless TKR: a 5-year prospective study. *Trans. Orthop. Res. Soc.*, 22: 235, 1997.
51. **Jacobs, J. J.; Urban, R. M.; Wall, J.; Black, J.; Reid, J. D.; and Veneman, L.:** Unusual foreign-body reaction to a failed total knee replacement: simulation of a sarcoma clinically and a sarcoid histologically. A case report. *J. Bone and Joint Surg.*, 77-A: 444-451, March 1995.
52. **Jacobs, J. J.; Skipor, A. K.; Black, J.; Hastings, M. C.; Schavocky, J.; Urban, R. M.; and Galante, J. O.:** Metal release and excretion from cementless titanium total knee replacements. *Trans. Orthop. Res. Soc.*, 16: 558, 1991.
53. **Jacobs, J. J.; Skipor, A. K.; Doorn, P. F.; Campbell, P.; Schmalzried, T. P.; Black, J.; and Amstutz, H. C.:** Cobalt and chromium concentrations in patients with metal on metal total hip replacements. *Clin. Orthop.*, 329S: S256-S263, 1996.
54. **Jacobs, J. J.; Urban, R. M.; Gilbert, J. L.; Skipor, A. K.; Black, J.; Jasty, M.; and Galante, J. O.:** Local and distant products from modularity. *Clin. Orthop.*, 319: 94-105, 1995.
55. **Jacobs, J. J.; Skipor, A. K.; Urban, R. M.; Black, J.; Manion, L. M.; Starr, A.; Talbert, L. F.; and Galante, J. O.:** Systemic distribution of metal degradation products from titanium alloy total hip replacements: an autopsy study. *Trans. Orthop. Res. Soc.*, 19: 838, 1994.
56. **Jandhyala, B. S., and Hom, G. J.:** Minireview. Physiological and pharmacological properties of vanadium. *Life Sci.*, 33: 1325-1340, 1983.
57. **Jones, D. A.:** *Principles and Prevention of Corrosion*, p. 45. New York, MacMillan, 1992.
58. **Jones, L. C.; Hungerford, D. S.; Kenna, R. V.; Braem, G.; and Grant, V.:** Urinary excretion levels of metal ions in patients undergoing total hip replacement with porous-coated prosthesis: preliminary results. In *Quantitative Characterization and Performance of Porous Implants for Hard Tissue Applications*, edited by J. E. Lemons. American Society for Testing and Materials Special Technical Publication 953, pp. 151-161. Philadelphia, American Society for Testing and Materials, 1987.
59. **Kummer, F. J., and Rose, R. M.:** Corrosion of titanium/cobalt-chromium alloy couples. *J. Bone and Joint Surg.*, 65-A: 1125-1126, Oct. 1983.

60. **Langard, S., and Norseth, T.:** Chromium. In *Handbook of the Toxicology of Metals*, edited by L. Friberg, G. F. Nordberg, and V. B. Vouk. Ed. 2, vol. 2, pp. 185-210. Amsterdam, Elsevier, 1986.
61. **Lee, S.-H.; Brennan, F. R.; Jacobs, J. J.; Urban, R. M.; Ragasa, D. R.; and Glant, T. T.:** Human monocyte/macrophage response to cobalt-chromium corrosion products and titanium particles in patients with total joint replacements. *J. Orthop. Res.*, 15: 40-49, 1997.
62. **Lewis, C. G., and Sunderman, F. W., Jr.:** Metal carcinogenesis in total joint arthroplasty. Animal models. *Clin. Orthop.*, 329S: S264-S268, 1996.
63. **Lucas, L. C.; Buchanan, R. A.; and Lemons, J. E.:** Investigations on the galvanic corrosion of multialloy total hip prostheses. *J. Biomed. Mater. Res.*, 15: 731-747, 1981.
64. **Mathiesen, E. B.; Ahlbom, A.; Bermann, G.; and Lindgren, J. U.:** Total hip replacement and cancer. A cohort study. *J. Bone and Joint Surg.*, 77-B(3): 345-350, 1995.
65. **Mathiesen, E. B.; Lindgren, J. U.; Blomgren, G. G. A.; and Reinhold, F. P.:** Corrosion of modular hip prostheses. *J. Bone and Joint Surg.*, 73-B(4): 569-575, 1991.
66. **Maurer, A. M.; Brown, S. A.; Payer, J. H.; Merritt, K.; and Kawalec, J. S.:** Reduction of fretting corrosion of Ti-6Al-4V by various surface treatments. *J. Orthop. Res.*, 11: 865-873, 1993.
67. **Meachim, G., and Williams, D. F.:** Changes in nonosseous tissue adjacent to titanium implants. *J. Biomed. Mater. Res.*, 7: 555-572, 1973.
68. *Medical Devices; Emergency Medical Services. Annual Book of ASTM Standards*, vol. 13.01. West Conshohocken, Pennsylvania, American Society for Testing and Materials, 1997.
69. **Memoli, V. A.; Urban, R. M.; Alroy, J.; and Galante, J. O.:** Malignant neoplasms associated with orthopedic implant materials in rats. *J. Orthop. Res.*, 4: 346-355, 1986.
70. **Merritt, K., and Brown, S. A.:** Biological effects of corrosion products from metal. In *Corrosion and Degradation of Implant Materials. Second Symposium*, edited by A. C. Fraker and C. D. Griffin. American Society for Testing and Materials Special Technical Publication 859, pp. 195-207. Philadelphia, American Society for Testing and Materials, 1985.
71. **Michel, R.; Hofmann, J.; Löer, F.; and Zilkens, J.:** Trace element burdening of human tissues due to corrosion of hip-joint prostheses made of cobalt-chromium alloys. *Arch. Orthop. and Trauma Surg.*, 103: 85-95, 1984.
72. **Michel, R.; Nolte, M.; Reich, M.; and Löer, F.:** Systemic effects of implanted prostheses made of cobalt-chromium alloys. *Arch. Orthop. and Trauma Surg.*, 110: 61-74, 1991.
73. **Mody, D. R.; Esses, S. I.; and Heggeness, M. H.:** A histologic study of soft-tissue reactions to spinal implants. *Spine*, 19: 1153-1156, 1994.
74. **Nyrén, O.; McLaughlin, J. K.; Gridley, G.; Ekblom, A.; Johnell, O.; Fraumeni, J. F., Jr.; and Adami, H.-O.:** Cancer risk after hip replacement with metal implants: a population-based cohort study in Sweden. *J. Nat. Cancer Inst.*, 87: 28-33, 1995.
75. **Pazzaglia, U. E.; Cecilian, L.; Wilkinson, M. J.; and Dell'Orbo, C.:** Involvement of metal particles in loosening of metal-plastic total hip prostheses. *Arch. Orthop. and Trauma Surg.*, 104: 164-174, 1985.
76. **Pazzaglia, U. E.; Minoia, C.; Cecilian, L.; and Riccardi, C.:** Metal determination in organic fluids of patients with stainless steel hip arthroplasty. *Acta Orthop. Scandinavica*, 54: 574-579, 1983.
77. **Pazzaglia, U. E.; Minoia, C.; Gualtieri, G.; Gualtieri, I.; Riccardi, C.; and Cecilian, L.:** Metal ions in body fluids after arthroplasty. *Acta Orthop. Scandinavica*, 57: 415-418, 1986.
78. **Peltier, L. F.:** *Fractures: A History and Iconography of Their Treatment*, pp. 114-167. San Francisco, Norman Publishing, 1990.
79. **Péoc'h, M.; Moulin, C.; and Pasquier, B.:** Systemic granulomatous reaction to a foreign body after hip replacement [letter]. *New England J. Med.*, 335: 133-134, 1996.
80. **Porter, D. A., and Easterling, K. E.:** *Phase Transformations in Metals and Alloys*, p. 17. New York, Van Nostrand Reinhold, 1981.
81. **Rostoker, W.; Galante, J. O.; and Lereim, P.:** Evaluation of couple/crevice corrosion by prosthetic alloys under in vivo conditions. *J. Biomed. Mater. Res.*, 12: 823-829, 1978.
82. **Sevitt, S.:** Corrosion of implants and tissue metallosis. In *Bone Repair and Fracture Healing in Man*, pp. 281-295. New York, Churchill Livingstone, 1981.
83. **Shetty, H. R., and Jacobs, C. H.:** Galvanic corrosion properties of 22-13 5/316L stainless steel couple in physiologic solution [abstract]. *Trans. Soc. Biomater.*, 10: 231, 1987.
84. **Sinibaldi, K.; Rosen, H.; Liu, S.-K.; and DeAngelis, M.:** Tumors associated with metallic implants in animals. *Clin. Orthop.*, 118: 257-266, 1976.
85. **Skinner, H.; Weinstein, A. M.; Clemow, A.; McPhillips-Meade, M.; Klawitter, J.; and French, G.:** Corrosion, materials characteristics and local tissue reaction associated with osteosynthesis devices, pp. 423-447. In *Proceedings of a Conference on Implant Retrieval: Material and Biological Analysis*. Special Publication 601. Gaithersburg, Maryland, National Bureau of Standards, 1980.
86. **Smethurst, E., and Waterhouse, R. B.:** Causes of failure in total hip prostheses. *J. Mater. Sci.*, 12: 1781-1792, 1977.
87. **Stulberg, B. N.; Merritt, K.; and Bauer, T. W.:** Metallic wear debris in metal-backed patellar failure. *J. Appl. Biomater.*, 5: 9-16, 1994.
88. **Sunderman, F. W.:** A pilgrimage into the archives of nickel toxicology. *Ann. Clin. Lab. Sci.*, 19: 1-16, 1989.
89. **Sunderman, F. W., Jr.:** Mechanisms of metal carcinogenesis. *Biol. Trace Element Res.*, 1: 63-86, 1979.
90. **Sunderman, F. W., Jr.; Hopfer, S. M.; Swift, T.; Rezuze, W. N.; Ziebka, L.; Highman, P.; Edwards, B.; Folcik, M.; and Gossling, H. R.:** Cobalt, chromium, and nickel concentrations in body fluids of patients with porous-coated knee or hip prostheses. *J. Orthop. Res.*, 7: 307-315, 1989.
91. **Sury, P.:** Corrosion behaviour of cast and forged implant materials for artificial joints, particularly with respect to compound designs. *Corrosion Sci.*, 17: 155-169, 1977.
92. **Svensson, O.; Mathiesen, E. B.; Reinhold, F. P.; and Blomgren, G.:** Formation of a fulminant soft-tissue pseudotumor after uncemented hip arthroplasty. A case report. *J. Bone and Joint Surg.*, 70-A: 1238-1242, Sept. 1988.
93. **Tarr, R. R.; Jorge, R.; Latta, L. L.; and Ghandur-Mnaymneh, L.:** Histopathology and metallurgical analysis of a removed Lane plate at 53 years postimplantation: a case report. *J. Biomed. Mater. Res.*, 17: 785-792, 1983.
94. **Urban, R. M.; Jacobs, J. J.; Gilbert, J. L.; and Galante, J. O.:** Migration of corrosion products from modular hip prostheses. Particle microanalysis and histopathological findings. *J. Bone and Joint Surg.*, 76-A: 1345-1359, Sept. 1994.
95. **Urban, R. M.; Jacobs, J. J.; Gavrilovic, J.; Tomlinson, M. J.; Black, J.; Turner, T. M.; and Galante, J. O.:** Dissemination of metal alloy particles to the liver and spleen of patients with total hip or knee replacement prostheses [abstract]. *Trans. Fifth World Biomater. Cong.*, 1: 660, 1996.

96. **Urban, R. M.; Jacobs, J. J.; Gilbert, J. L.; Rice, S. B.; Jasty, M.; Bragdon, C. R.; and Galante, J. O.:** Characterization of solid products of corrosion generated by modular-head femoral stems of different designs and materials. In *Modularity of Orthopedic Implants*, edited by D. E. Marlowe, J. E. Parr, and M. B. Mayor. American Society for Testing and Materials Special Technical Publication 1301, pp. 33-44. West Conshohocken, Pennsylvania, American Society for Testing and Materials, 1997.
97. **Venable, C. S., and Stuck, W. G.:** *The Internal Fixation of Fractures*. Springfield, Illinois, Charles C Thomas, 1947.
98. **Visuri, T., and Koskenvuo, M.:** Cancer risk after McKee-Farrar total hip replacement. *Orthopedics*, 14: 137-142, 1991.
99. **Visuri, T.; Pukkala, E.; Paavolainen, P.; Pulkkinen, P.; and Riska, E. B.:** Cancer risk after metal on metal and polyethylene on metal total hip arthroplasty. *Clin. Orthop.*, 329S: S280-S289, 1996.
100. **Wapner, K. L.:** Implications of metallic corrosion in total knee arthroplasty. *Clin. Orthop.*, 271: 12-20, 1991.
101. **Weinstein, A.; Amstutz, H.; Pavon, G.; and Franceschini, V.:** Orthopedic implants — a clinical and metallurgical analysis. *J. Biomed. Mater. Res. Symp.*, 7: 297-325, 1973.
102. **Willert, H.-G.; Brobäck, L.-G.; Buchhorn, G. H.; Jensen, P. H.; Köster, G.; Lang, I.; Ochsner, P.; and Schenk, R.:** Crevice corrosion of cemented titanium alloy stems in total hip replacements. *Clin. Orthop.*, 333: 51-75, 1996.
103. **Williams, D. F.:** Biological effects of titanium. In *Systemic Aspects of Biocompatibility*, pp. 169-177. Edited by D. F. Williams. Boca Raton, Florida, CRC Press, 1981.
104. **Williams, D. F., and Meachim, G.:** A combined metallurgical and histological study of tissue-prosthesis interactions in orthopedic patients. *J. Biomed. Mater. Res.*, 8: 1-9, 1974.
105. **Winter, G. D.:** Tissue reactions to metallic wear and corrosion products in human patients. *J. Biomed. Mater. Res.*, 8: 11-26, 1974.
106. **Winter, G. D.:** Wear and corrosion products in tissues and the reactions they provoke. In *Biocompatibility of Implant Materials*, pp. 28-39. Edited by D. Williams. London, Sector, 1976.
107. **Wisbey, A.; Gregson, P. J.; Peter, L. M.; and Tuke, M.:** Effect of surface treatment on the dissolution of titanium-based implant materials. *Biomaterials*, 12: 470-473, 1991.
108. **Woodman, J. L.; Black, J.; and Jiminez, S. A.:** Isolation of serum protein organometallic corrosion products from 316LSS and HS-21 in vitro and in vivo. *J. Biomed. Mater. Res.*, 18: 99-114, 1984.
109. **Woodman, J. L.; Black, J.; and Nunamaker, D. M.:** Release of cobalt and nickel from a new total finger joint prosthesis made of vitallium. *J. Biomed. Mater. Res.*, 17: 655-668, 1983.
110. **Woodman, J. L.; Jacobs, J. J.; Galante, J. O.; and Urban, R. M.:** Metal ion release from titanium-based prosthetic segmental replacements of long bones in baboons: a long-term study. *J. Orthop. Res.*, 1: 421-430, 1984.