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EDITORIAL

Francesco Pipino

The bone-prosthesis interaction

Introduction

The bone-prosthesis interaction is a dynamic succession of mechanical and biological phenomena, provoked by the implant of a joint endoprosthesis, which follow and overlap each other in time to determine the success and longevity of the prosthesis itself. The entity, typology and significance of these phenomena have been accurately studied in total hip prostheses. In light of current knowledge, they must be recognized to be representatives of a complex process which is not restricted to periprosthetic bone but which also involves the whole hip joint, the musculoskeletal system and the entire organism.

The prosthesis is the catalyst of this process. It modifies the geometric configuration and the mechanical environment of the joint in such a way as to influence both muscle function and load transfer to the bone. Furthermore, it introduces extraneous materials, organized in mechanical systems of trunnions and couplings, which may generate wear and corrosion debris with potential properties of cytotoxicity and immuno-sensitization.

F. Pipino (✉)
Orthopedics Clinic,
University of Genoa, Genoa, Italy
Tel.: +39-010-3537759
Fax: +39-010-3537379
E-mail: fpipino@smartino.ge.it

Periprosthetic bone and sometimes the whole organism react to these changes with biologic, mechanic and functional responses, which condition the fate of the implant during its life-span. On the basis of such responses the prosthesis will be recognized as a different but integral part of the host bone or, on the contrary, it will behave as a foreign body and will go to its failure.

The bone-prosthesis interaction consists of the following aspect:

1. *Mechanical stimulation*, due to the characteristics of design, elasticity (changes in magnitude and direction of the stresses applied to bone) and geometric configuration (changes in the static and kinematic equilibrium of the joint) of the prosthetic device;
2. *Biological bone responses to mechanical stimulation*, with specific phenomena involving both the bone-prosthesis interface (bone growth) and the periprosthetic bone (bone remodeling);
3. *Immunological stimulation,* by constructive biomaterials as a result of wear debris release;
4. *Immunological reactions (local and general),* provoked by particle and ionic debris.

Prosthetic features and mechanical stimulation

Changes in loads applied to bone

Bone is normally subject to stresses and strains which are due to weight bearing and movements and which determine its structural organization during life. In the hip joint, especially in the proximal femur, the moment of applied loads is mainly dependent on body weight, articular geometry and muscular activity. Throughout the joint, stresses and strains are transferred to cortical and spongy bone with a tendency to concentrate in the calcar region and discharge themselves distally. The insertion of a stemmed prosthesis into the femur modifies this mechanical pattern by introducing into the joint a new anatomic-functional element with its own features of geometry, modulus of elasticity and tolerance to loads, which may be very different from the physiological ones (Fig. 1a).

To contain these mechanical changes, the shape and elasticity of prosthetic components must meet certain requirements, such as:

- To be stable in the spatial planes;
- To contain and absorb stresses and strains and to transfer them uniformly to the surrounding bone, by decreasing their natural tendency to concentrate in the distal cortical bone;
- To minimize wear and to optimize the joint motion.

The *femoral stem* is the critical component, because it is particularly exposed to torque and bending moments, which are difficult to stop and are responsible for micromotion at the bone-prosthesis interface. Micromotion characterizes every prosthetic stem, especially the uncemented ones. When the stem is initially well stable, early micromotion is low (30–50 μm); it may decrease within 1–2 years from operation, because of stem stabilization due to bone growth. On the contrary, if early micromotion is greater, for failure of initial stem fixation, it may gradually increase and cause lack of osseointegration and implant loosening.

Fixation and initial stability of the stem may be entrusted either to cement, acting as a filler and a shock-absorber or, in uncemented stems, to the press-fit or other design constraints, such as neck anteversion, anti-rotational wings, surface ribs and grooves. It is my firm belief that the maximal torsional stability can be achieved (1) by means of the bone-adapted stem design (stem helitorsion), which allows the stem to adapt itself to the proximal femur morphology and reach stability by adhering to the medial and anterior cortex and (2) especially, by means of the preservation of the femoral neck (Fig. 1b). The latter situation realizes in the proximal femur two bony cylinders, angled on the bias, in which the stem is contained and made unable to rotate: the cylinder representing the femoral neck acts as a lateral lever arm, which is opposed to torsional stresses and is subjected to compressive loads applied to the neck cortex (Fig. 1c).

In order to achieve adequate stress transfer, with minimized proximal by-pass of loads and distal concentration, it is necessary to limit the natural implant stiffness by using stems with dimensions similar to that of the femoral canal to be filled, materials with modulus of elasticity closest to that of the bone (30 GPa), and osteoconductive coatings applied to the proximal part of the stem only. However, the essential issue is modulating the elasticity of the whole bone-prosthesis complex, by respecting the structure of the trajectorial systems of loads distribution and by searching for the prosthetic fit and fill in the metaphyseal spongy bone. The latter may be compared to a spring system which allows and controls stem micromotion to converge it in a physiological direction.

For these reasons, I prefer stems having a slim proximal part; this preserves the spongy bone and compresses it to achieve stability with press-fit. In addition, I choose stems which have a distal part that can simply adhere to the cortical bone without filling the femoral canal; this avoids dangerous gain of the stem tip (Fig. 1d).

Changes in static and kinematic equilibrium of the joint

In normal conditions, the hip joint lies in a state of static and kinematic equilibrium. This equilibrium retains the magnitude and direction of applied stresses and relies on muscle function to assure normal gait and physiological range of motion.

The static and kinematic equilibrium of the hip depends on the synergic activity of select groups of pelvi-trochanteric muscles which co-operate to center the femoral head within the acetabulum and to maintain the spatial position of the proximal femur. The vertical pelvi-trochanteric muscles or abductor muscles, primarily the gluteus medius, “pull” the femoral head in the acetabulum and translate it upward and laterally. The medial pelvi-trochanteric muscles, primarily the external rotators, act synergistically but in opposition to the abductors, by producing a transversal force that “pushes” the femoral head into the acetabulum. In this way, the pelvi-tronchanteric muscles play an important role as stabilizers of the hip joint (Fig. 1e).

Biomechanically, the strength (moment) of the abductor muscles balances the moment of body weight and controls the resulting *joint reaction force,* i.e. the magnitude of compressive loads applied to the femoral head. In contrast, the strength (moment) of the medial pelvi-trochanteric muscles retains the *bending moment* on the middle of the diaphysis. Muscle strength depends on muscle tension, which can be represented by the length of the muscle lever arm. The latter is closely related to the parameters of hip geometry, in particular the CCD angle and the femoral offset.

Every prosthetic stem device modifies the original geometry of the hip, as a result of its inherent geometry or its placement. Thus, the prosthetic stem provokes variations in muscle lever arms and, consequently, changes in magnitude and direction of the applied loads, especially joint reaction force and bending moment. A decreased femoral offset, due to valgus-shifted insertion or poor geometry of the stem (CCD angle > 135°; inherent offset < 35 mm) makes the femur medialized, with the shortening of the lever arms and loss of tension of both abductor and external rotator muscles. This situation can induce implant instability and affect the static and kinematic equilibrium of the hip joint, by worsening muscle function and increasing the joint reaction force, with higher risk of biomaterial wear for friction. On the contrary an increased femoral offset, due to varus-shifted placement or inherent varus CCD angle, defines a more lateral position of the femur, with lengthening of lever arms, improved muscular strength and decreased joint reaction force. Despite these mechanical advantages, there is also a parallel increase of torque and bending moments, advising the use of varus stems.

The design and geometric configuration of most of the stems currently used (130°–135° CCD angle; inherent offset, 35–38 mm) realize a sufficient femoral lateralization

and represent a good biomechanical compromise relating to Pauwel's balance, magnitude of applied loads, articular stability and muscular efficiency. However, only the preservation of the femoral neck, by maintaining the CCD angle and natural femur offset, may determine a biomechanical situation closest to the static and kinematic equilibrium of the hip, with retaining of static loads and adequate muscle tension to normal movement and gait (Fig. 1f). Furthermore, the reduction of the forces across the hip joint reduces wear and debris release (Fig. 1g).

The biologic response of bone to mechanical stimulation

The morphology and structure of periprosthetic bone adapt to the mechanical changes induced by the prosthesis through a series of superimposing processes of resorption, formation of new bone and remodeling according to Wolff's law or, more generally, according to the laws which regulate the biodynamics of the functional unity of bone. The functional unity of bone is represented by BMU (bone multicellular unit), with its different cellular populations (osteocytes, osteoblasts and osteoclasts). In normal bone, the coordinate activity of BMUs leads to the physiological substitution of old bone, impaired by wear, with new-formed bone of better mechanical quality.

The transduction mechanism of the physical stimulus in a biological impulse is still unknown. Some experimental data suggest that this transformation takes place in the osteocytes. Indeed, these cells show both an increased synthesis of proteins and a re-organization of matrix proteoglycans after the application of intermittent compressive loads. Membrane phospholipases might be the real transducers, by promoting the synthesis of yet unidentified chemical substances.

In total hip replacement, the biological response modulated by BMUs can typically be observed in the proximal femur through two series of phenomena:

1. Early phenomena of new bone formation at the bone-prosthesis interface (bone growth).
2. Later phenomena of removal and replacement of periprosthetic bone (bone remodeling).

Bone growth

The early phenomena are especially evident in uncemented implants. They consist in the deposition of mineralized bone in the space between the host bone and the stem surface (bone growth). Proceeding from the host bone to the prosthesis, this space is initially occupied by the following structures:

- Necrotic but structurally intact bone, produced after surgical procedures (especially milling, washing and cleaning of bone cavities);
- Fragments of lamellar bone, marrow, blood and clots;
- Surface of the stem, with the conversion layer, which may be represented by cement, metal coating, bioactive coating or other materials.

Immediately after implantation, the prosthesis surface is modified for the deposition of a layer of glycoproteins. Simultaneously, the vascular invasion of the bone-prosthesis gap takes place and, as happens in fracture healing, the deposition of an extracellular matrix composed of proteoglycans and collagen fibers begins. Due to the interaction with osteoblasts this matrix changes into slender and fragile lamellas of woven bone, which can be observed one month after the operation. These lamellas arise from the sites of maximal adhesion between bone and prosthesis and develop in a centripetal way towards the implant surface.

In time, immature woven bone converts into mature lamellar bone with thicker and stronger lamellas. Within 12–18 months, this process leads to prosthesis osseointegration (Fig. 1h). However, bone growth can only occur when the stem is stable and well-fitting to the surrounding bone, i.e. when micromotion at the interface due to the applied loads is minimal (< 30–70 μm), and the gap between bone and prosthesis is narrower than 1.5–2.0 mm.

Bone growth occurs due to both *osteoinduction*, i.e. the intrinsic ossification of the bone-prosthesis interface, and *osteoconduction*, i.e. the progressive substitution of the gap content with newly formed trabeculae of mineralized bone originated from endosteal surface. For this reason, bone growth needs *osteo-conductive surfaces*, either porous surfaces with average pore dimensions of 50–400 μm, or microtextured blasted surfaces which permit osteogenesis over (bone on-growth) and within (bone in-growth) the structure. Furthermore, bone growth is accelerated and enhanced by *osteo-inductive bioactive coatings* which can promote the formation of bone as a result of the release of calcium and phosphate ions in the extracellular matrix.

The bioactive compounds mainly employed in the prosthetic implant coatings belong to the calcium-phosphate family of biomaterials; tricalcium phosphate and hydroxyapatite are among the most important. Hydroxyapatite in particular, after its long exposition to extensive experimental and clinical testings, has achieved excellent long-term results of biocompatibility and promotion of osseointegration.

Nonetheless, some new compounds are currently being tested for their promising biologic properties, such as brushite (dicalcium-phosphate) which is hydroxyapatite-like but has a different calcium to phosphate ratio (1.20 instead of 1.67), fluorapatite, bioactive polymers and the newest porous tantalum. A great interest is also arising for the potential clinical applications of the transforming

growth factor beta, a family of proteins with osteoinductive and enhancing effects on bone formation.

The amount of bone growth, expressed in terms of extent and volume-fraction, significantly varies according to the prosthetic design, coating features, method of evaluation and anatomical sites that are examined. Several histological studies, especially the most recent of implants retrieved from autopsy of humans, suggest that bone growth progressively increases in time and may reach a wide extent, although it never seems to reach the magnitude experimentally observed in some animal models. However such a wide bone growth as to cover the whole porous prosthetic surface might make the bone-prosthesis complex stiff and prevent the uniform stress distribution to bone.

Bone remodeling

Later phenomena (bone remodeling) begin in the months following the operation but persist throughout implant life. Although bone remodeling is more evident in uncemented prostheses, it characterizes every type of implant and consists in a dynamic biologic sequence of apposition and removal of bone tissue closely related to mechanical stimulation. Bone remodeling involves the whole host bone and represents the real host bone response to the prosthesis; this conditions the long-term survival much more than interface bone growth does. Bone remodeling develops during two different periods of time:

- Early remodeling occurs within the first six months. In this period, the process of new bone formation prevails and proceeds proportionally to the bone growth extension and the increase in prosthetic stability.
- Late remodeling, where resorption phenomena and structural re-organization prevail, according to Wolff's law.

Relating to mechanical conditions (prosthetic stability, stress distribution to bone), bone remodeling may result in a well-balanced process of resorption and formation of new bone that preserves and renews, the host bone by carrying its structure back to the physiological state. However, in certain conditions, it may induce morpho-structural bone changes (e.g. atrophy, hypertrophy, sclerosis) in host bones. Sometimes, in systems of forces very different from the natural ones, bone remodeling may lead to the complete breakdown of host bone structure.

The first pattern of bone remodeling occurs only when the femoral stem is stable and when loads are transferred to the bone in a physiological way. The radiographic findings of balanced bone remodeling are characterized by the normalization of structure and thickness of the cortical bone and by the appearance of spot-welds, images of ossification at the bone-prosthesis interface which appear as bridgings of dense bone surrounding the implant surface.

If the stem is stable but results in increased stiffness of the bone-prosthesis complex, due to either its design (press-fit shape, full-coated surface, materials with lower modulus of elasticity) or modes of implantation (oversized implant, lack of respect of bony structures, periosteal and endosteal circles and bone marrow), the natural tendency of loads to by-pass the proximal femur and concentrate in the distal cortical bone is enhanced. This modality of stress transfer causes *stress-shielding*, adaptive bone remodeling characterized by hypertrophy of the cortical and spongy bone of the proximal femur, which undergoes a reduced mechanical stimulation (by-pass of loads), combined with cortical hypertrophy at the stem tip, which is on the contrary overloaded (stress concentration). Severe stress-shielding causes pain. Although some studies have not attributed it to an increased incidence of implant loosening in the first 10 years after operation, stress-shielding remains a source of concern regarding the fate of the implant. However, proximal osteopenia due to by-pass of loads is a common feature in most implants. In fact, proximal osteopenia may be responsible for the decrease in periprosthetic bone mineral density that characterizes every uncemented implant during the first 1–2 years (Fig. 1i).

In unstable implants (due to either inadequate design or inaccurate implantation), micromotion due to inferior fixation prevents bone growth and osseointegration and promotes the formation of fibrous tissue at the bone-prosthesis interface. Radiographically, it results in periprosthetic lines of *radiolucency* and *demarcation*, which are the typical finding of bone remodeling in less stable implants.

Radiolucency appears as periprosthetic lines having variable thickness and "empty" transparent look. This represents the bone-prosthesis gap completely filled by unmineralized fibrous tissue. A thin radiodense edge is generally present at the periphery. This represents the process of ossification for osteoconduction that, as happens in nonunion, has been blocked for an excess of micromotion.

Thinner lines (< 1 mm) are not evolutive and characterize the secondary stabilization which has been reached by the implant because of fibrous integration. Larger lines, on the contrary, may evolve towards the so-called osteosclerotic room and, in combination with de-structuration of the cortical bone (cancellization) and formation of a pedestal at the stem tip, they typify the radiographical aspect of loosened prosthesis.

Demarcation lines are periprosthetic lines limited at their periphery by a thin radiodense edge, but they appear less diaphanous than radiolucency lines do. They occur when an implant, initially lacking stability due to subsidence and bending, finds a new position that is mechanically more advantageous. In this situation osteoconduction, which has been stopped at the periphery of the implant, can restart and lead to osseointegration.

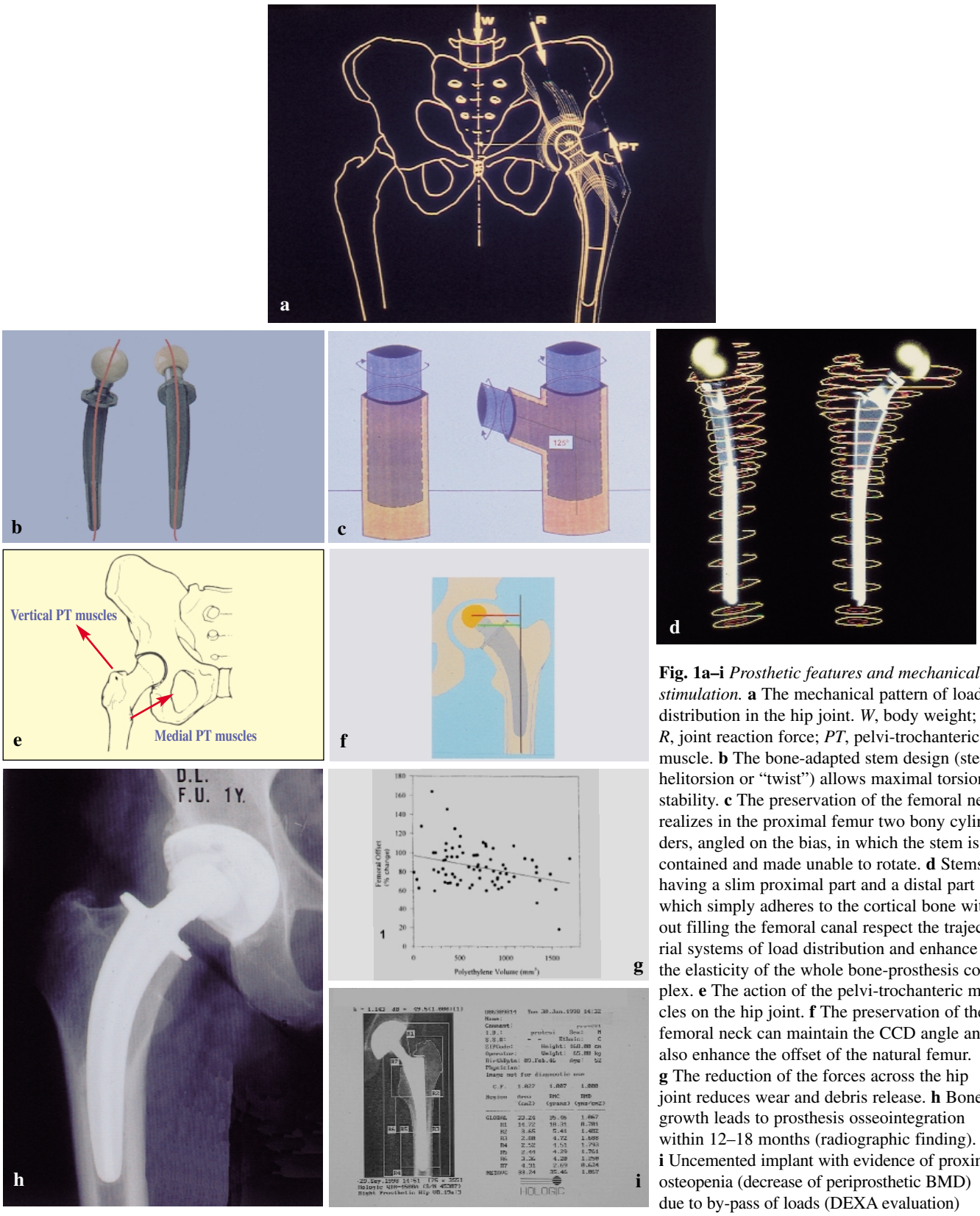

Fig. 1a–i *Prosthetic features and mechanical stimulation.* **a** The mechanical pattern of load distribution in the hip joint. *W*, body weight; *R*, joint reaction force; *PT*, pelvi-trochanteric muscle. **b** The bone-adapted stem design (stem helitorsion or "twist") allows maximal torsional stability. **c** The preservation of the femoral neck realizes in the proximal femur two bony cylinders, angled on the bias, in which the stem is contained and made unable to rotate. **d** Stems having a slim proximal part and a distal part which simply adheres to the cortical bone without filling the femoral canal respect the trajectorial systems of load distribution and enhance the elasticity of the whole bone-prosthesis complex. **e** The action of the pelvi-trochanteric muscles on the hip joint. **f** The preservation of the femoral neck can maintain the CCD angle and also enhance the offset of the natural femur. **g** The reduction of the forces across the hip joint reduces wear and debris release. **h** Bone growth leads to prosthesis osseointegration within 12–18 months (radiographic finding). **i** Uncemented implant with evidence of proximal osteopenia (decrease of periprosthetic BMD) due to by-pass of loads (DEXA evaluation)

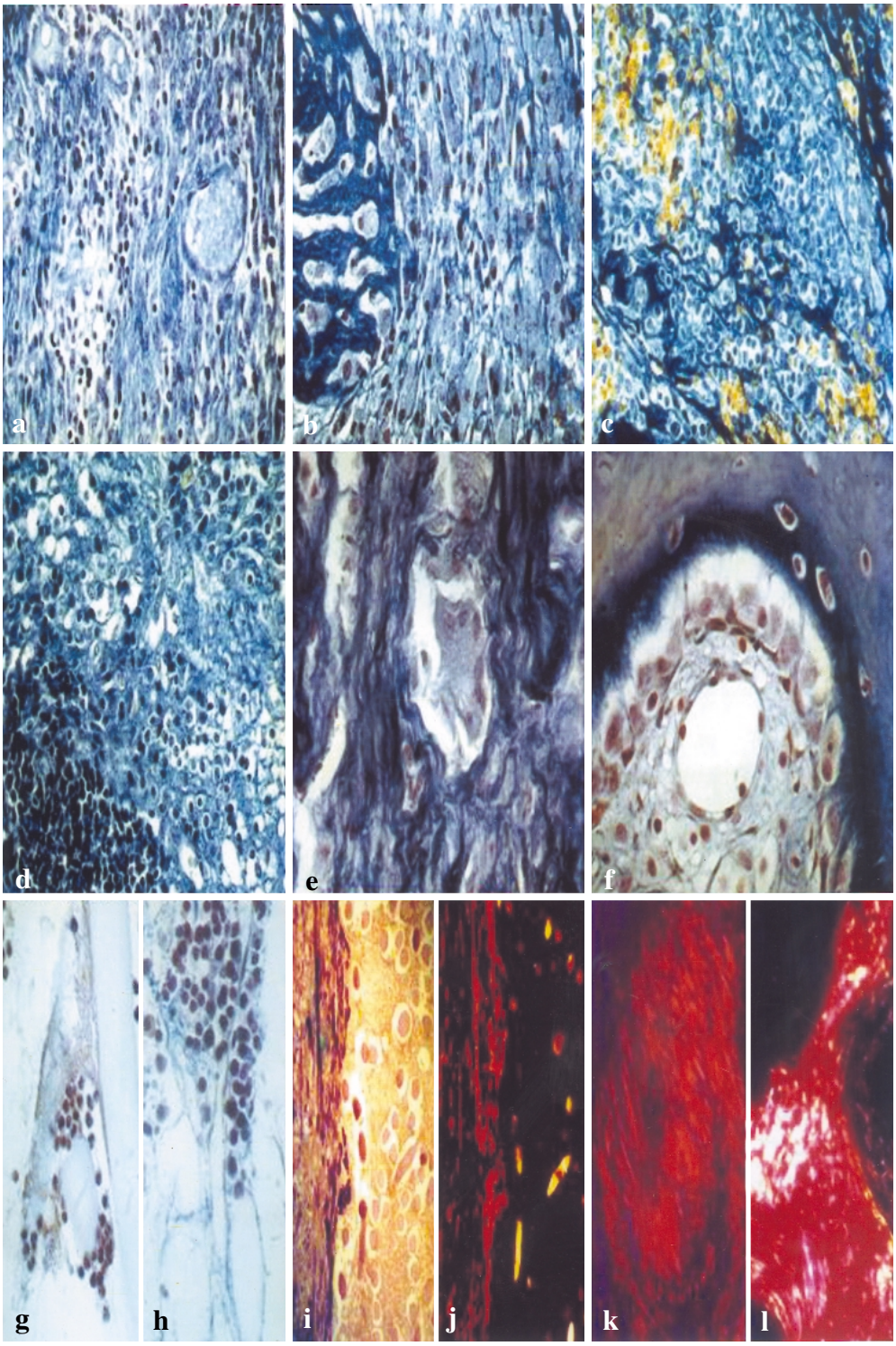

Fig. 2a-l *Biologic responses due to immunological stimulation at the bone-prosthesis interface.* **a** Infiltrate of macrophages in a widely vascularized fibrous extracellular matrix (t OPA 120X). **b** Epitheliod cells in palasade formation in several layers (t OPA 120X). **c** Lymphocyte and monocyte infiltrate with hemorragic area (yellow-colored) (t OPA 120X). **d** Lymphocyte and monocyte infiltrate with epitheliod cells. Macrophages indicate a marked metallosis (t OPA 120X). **e** Giant cell (Langhans) within a dense fibrous matrix (t OPA 120X). **f** Osteolysis area (t OPA 160X). **g, h** Typical infiltrates without fibroplasic reaction: polymorphonucleated cells (t OPA 120X) (g), lymphocytes and monocytes (t OPA 120X) (h). **i, j** Polyethylene particulate debris: finding in bright-field (Red-Sirius 120X) (i), finding in polarized light (Red-Sirius 120X) (j). **k, l** Calcification area observed in polarized light: initial phase (Red-Sirius 160X) (k), advanced phase (Red-Sirius 120X) (l). (Courtesy of G.F. Tajana, Napoli)

Immunological stimulation

Material wear, a result of debris release, is the main cause of local and general immunological stimulation that the prosthesis may induce.

Materials used in biological implants (e.g. metal alloys, ceramics and polyethylene) have been selected for *biocompatibility* (i.e. theoretic inability to evoke adverse reactions), *mechanical strength* and *chemical stability*. However, the release of particulate and ionic debris from wear, fretting and corrosion is well documented in all prosthetic implants.

Potential sources of debris are represented by the articular couple (femoral head-socket), the interface between metallic shell and liner of the cup, screws holes, Morse taper trunnion femoral head connection, and the interface between coating and metal surface. Debris production occurs through different processes. *Polyethylene debris* (average 1–20 μm) is generated by adhesion, delamination, abrasion, interpositioning of particles (i.e. cement, hydroxyapatite) in the joint space (third body wear) or, rarely, by fatigue. *Metal debris* (0.5–20 μm) or *debris from coating materials* (e.g. pure titanium, hydroxyapatite) arise by fretting, galvanic corrosion or de-bonding from the substrate. Some recent observations have demonstrated that cement may also produce debris by abrasion at the interfaces either with bone or prosthesis, especially if the surface of the latter is irregular or rough.

Depending on their size and chemical composition, debris particles may elicit an inflammatory, cell-mediated response. This results in either a foreign-body giant-cell granuloma or a massive release of osteolytic factors affecting bone biology and metabolism. In contrast, dissolved ionic debris, generated by galvanic corrosion of metals, may pass into the blood circulation and cause toxic and immunoallergic phenomena.

The biologic response of bone (and human organism) to immunological stimulation

Bone biology may be influenced by mechanical stimulation as well as by the production of debris due to the wear and corrosion of biomaterials. Depending on the quantity, size, volume and composition, debris may have a considerable reactivity which may be both local and general. Relating to host sensitivity, debris may evoke a dramatic biologic reaction with cellular and tissular components.

Osteolysis with destruction of periprosthetic bone is the most common consequence. Debris particles migrate into the "peri-prosthetic effective joint space" where, depending on their size, they induce either a foreign-body giant cell response (larger particles) or a mononuclear cell response (smaller particles). Both foreign-body and mononuclear cell response produce an inflammatory fibrous tissue membrane mainly composed of macrophages, giant cells, fibroblasts and some lymphocytes (Fig. 2a-c, e, f, k, l).

The smallest particles are phagocytized by macrophages that release chemical substances with inflammatory and degradative action, in particular the cytokines interleukin (IL)-1b, IL-6, tumor necrosis factor (TNF), platelet-derived growth factor (PDGF), and prostaglandins (PG) E and F. These immunomediators stimulate the activation and differentiation of osteoclasts. At the same time they inhibit osteoblast activity by decreasing the biosynthesis of types I and III collagen and by promoting hyaline degeneration and cell necrosis. Simultaneously fibroblasts, recruited by prostaglandins into the osteolytic areas, enhance the production of metalloproteinases of the extracellular matrix and begin to produce a fibrous tissue that rapidly fills the lytic zone.

The development of the periprosthetic membrane and the following bone resorption cause loss of implant stability and, finally, its complete loosening. This cascade of events is known as *debris disease* and it can occur with either cemented or uncemented implants. Although debris disease was thought to be due to cement or polyethylene particles, it can really be evoked by every kind of particle, depending more on their dimension than chemical composition. Many in vivo and in vitro experimental studies have demonstrated that small polyethylene particles are particularly dangerous because of their number and documented actions of both increased bone resorption and net bone formation inhibition. The presence of polyethylene particulate debris in periprosthetic tissue is associated with foreign-body reaction, chronic inflammation and extensive formation of fibrous tissue (Fig. 2i, j).

After being phagocytized by macrophages, Co-Cr particles (and even Ti particles), which once were considered to be biologically inert, have the same cytoxicity and potentiality as producing osteolysis of polyethylene debris. However, their specific action seems to be the toxic inhibition of net bone formation.

In particular, CoCr particles mainly provoke a granuloma with dense infiltrates of macrophages, multinucleated giant cells and lymphocytes sometimes organized in large nodules. In addition, many cells present hyaline degeneration and necrosis, suggestive of a toxic effect (Fig. 2g, h). Due to this cellular reaction, tissues can macroscopically appear "stuffed" and "blackish" (metallosis) (Fig. 2d).

In addition to the effect on bone biology, biomaterial debris may also provoke general and local adverse allergic reactions in subjects with a diathesis to allergies induced by metals or cement. General reactions are due to the passage of chromium, cobalt or nickel ions or metacrylate polymers into the blood circulation or periprosthetic tissue. Local reactions, the importance of which has recently been emphasized, take place at bone-prosthesis interface with formation of a fibrous membrane containing numerous lymphocytes. These reactions can lead to infection of the implant. As a matter of fact, the final effects of wear debris (from polyethylene, metals, alumina, zirconia or hydroxyapatite) on periprosthetic bone differentiation and remodeling are still not clearly known.