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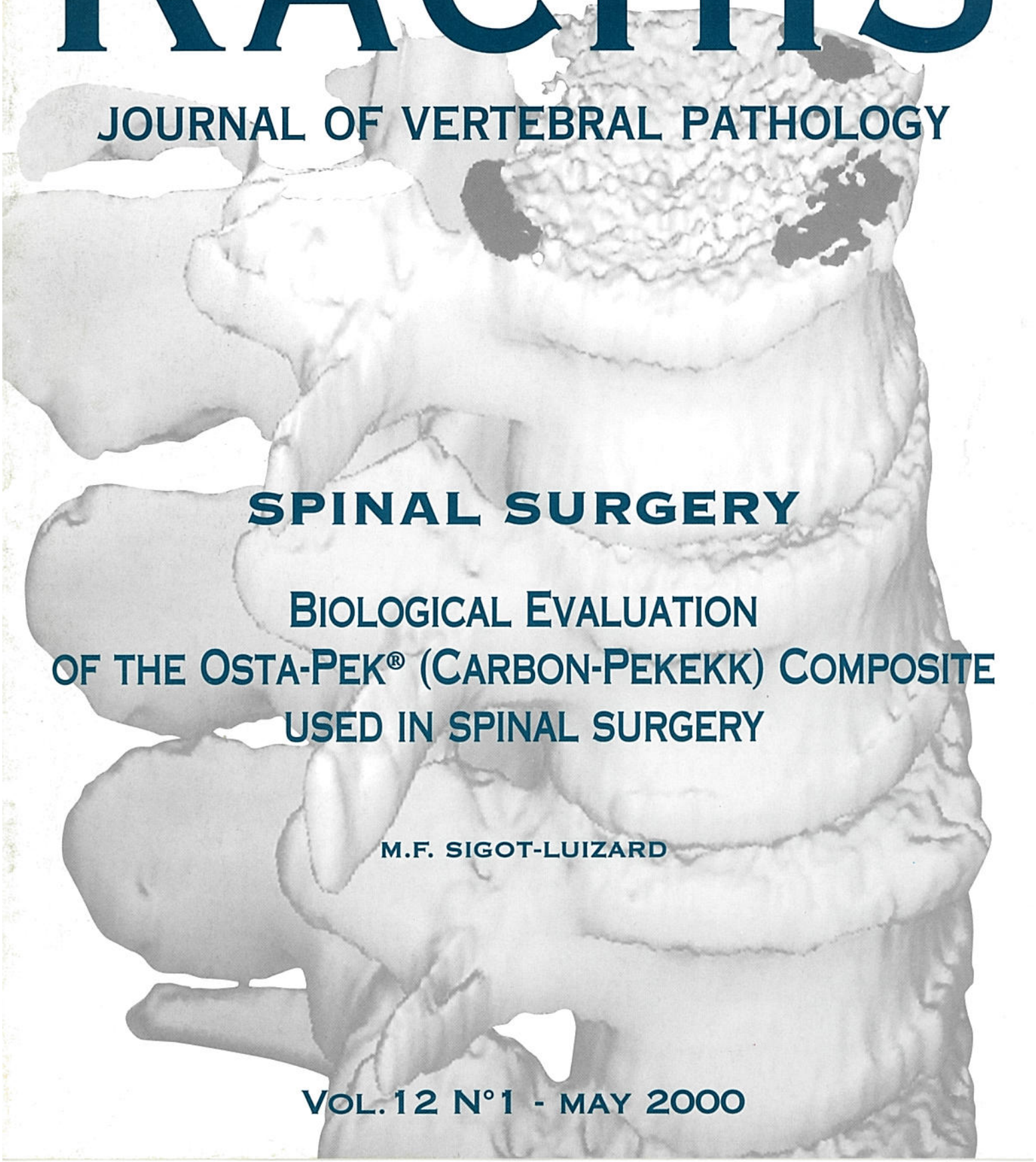

SPINAL SURGERY

BIOLOGICAL EVALUATION OF THE OSTA-PEK® (CARBON-PEKEKK) COMPOSITE USED IN SPINAL SURGERY

M.F. SIGOT-LUIZARD

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BIOLOGICAL EVALUATION OF THE OSTA-PEK® (CARBON-PEKEKK) COMPOSITE USED IN SPINAL SURGERY

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In recent years the use of interbody cages has made it possible to improve the usual intervertebral fusion technique recommended by R.B. Cloward (1). These implants are designed to receive a graft and to separate their mechanical and biological functions in order to allow a better fusion rate and better biomechanical stability, with the resultant anticipation of better clinical results (2). The materials currently used for these implants are primarily coated or uncoated titanium alloys or polymers with or without carbon reinforcement (3). The carbon composite polymer has two advantages over titanium and other materials used. On the one hand, its radiolucency allows the osseous repair to be monitored by standard radiographic methods. On the other, its modulus and of elasticity and structure makes it possible to build an implant with stiffness very close to a specific bone. These mechanical characteristics protect the bone graft from degeneration and prevents stress sheilding under load (4). Some of these implants are currently on the market, but none of these proposed carbon composites are exactly the same. A change in the ratio of the different components, in the orientation of the fibers or in the manufacturing process can result in a significant change in the biomechanical performance of the composite (5), with a consequent possible change in its biological properties. Moreover, such a change to obtain optimal performance in a given application does not necessarily mean that same performance will be achieved in another application. The composition, as well as the mechanical and biological properties of all implantable products, must therefore be clearly defined in order to guide the surgeon in choosing the best implant for a given application.

The purpose of this paper is to describe the studies carried out on a carbon composite polymer, a product called Osta-Pek®, in order to demonstrate its biocompatibility. This property is a complex interface phenomenon, defined as "the ability of a material to be used with an appropriate response in the host for a specific application" (6), a definition that emphasizes the important idea of specificity that depends on the material as well as on the host tissue. In effect, all these mechanisms involved in the material/tissue interface will depend on the origin of the material in determining its mechanical and chemical properties, as well as on its use in determining sites and differing lengths of implantation times, and therefore different biological reactions *(fig. 1)*.

Moreover, in the last 15 years the production of new materials has been directed more and more toward taking their biological performance into consideration. The result was a first generation of materials that were inert, tolerated by tissues (non-cytotoxic) and offering only technical performance, followed by a second generation of materials that are not only tolerated but

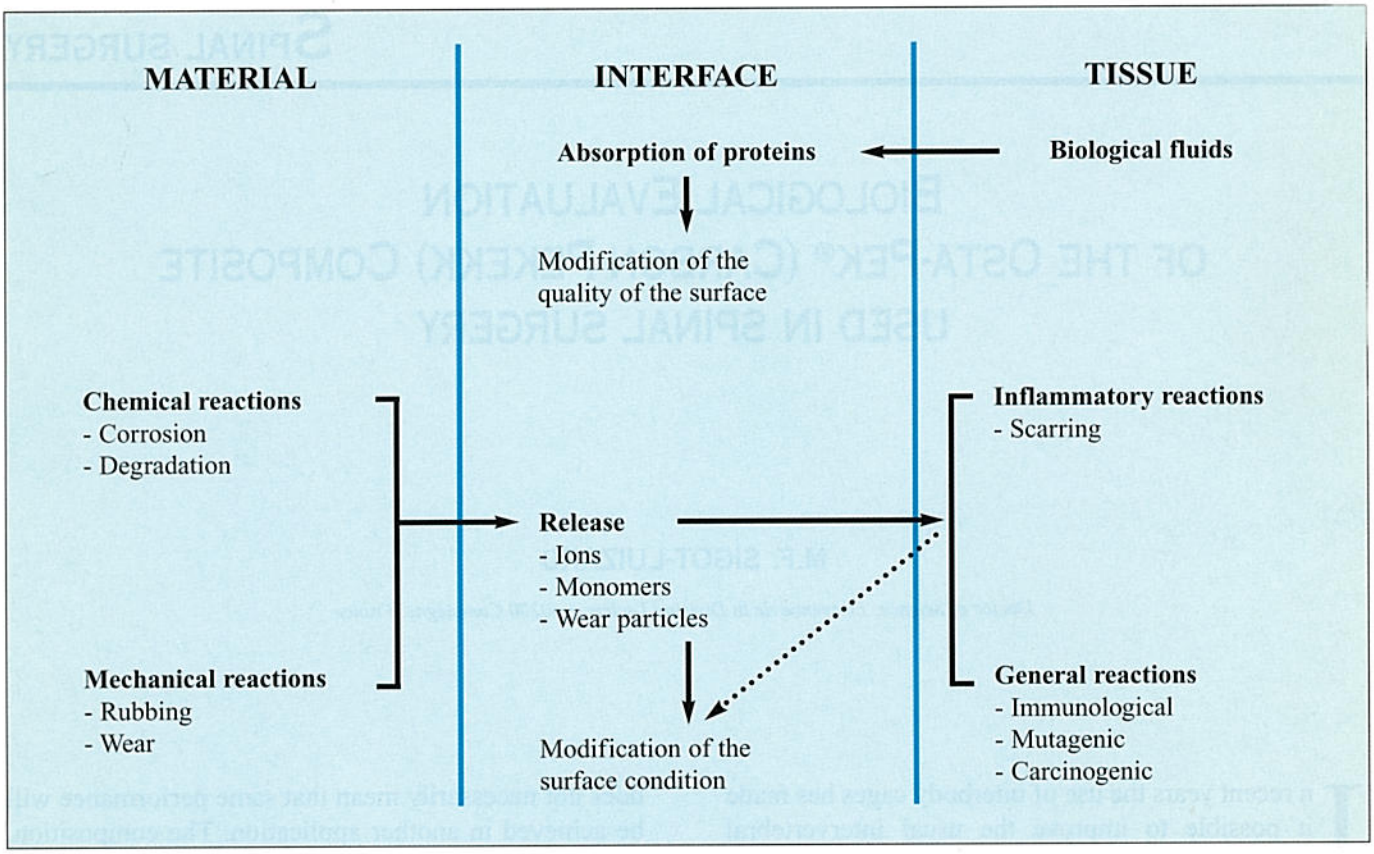

Figure 1 : Diagram of reactions at the material / tissue interface.

also accepted by the tissues (cytocompatible), and which can even actively participate in their integration into the surrounding tissues (biofunctional), thus offering a more or less important specific biological performance. Biocompatibility is therefore a multifactorial phenomenon that is complex and dynamic, as well as being difficult to evaluate (7). According to current regulations, it is essential that any implant meet the following criteria : effectiveness (suitability for the use and for the required biological function), safety (no health risks for the patient), and quality. There are a number of standard tests recommended by European and international standardization that make it possible to evaluate these mechanical, chemical, physico-chemical and biological properties that define these biocompatibility criteria.

Figure 2 : Co-Ligne cages made of Osta-Pek®.

In this paper we will only deal with the biological aspect of this biocompatibility, and because of the new requirements mentioned above, the evaluation of the Osta-Pek® composite was done twice. We first determined its non-toxicity based on current European and international standards (EN-ISO 10,993). Then in a second stage, we endeavored to show its good acceptance by the surrounding tissues, and in particular by the osseous tissue by using specific, appropriate experimental protocols that do not necessarily correspond to standard tests.

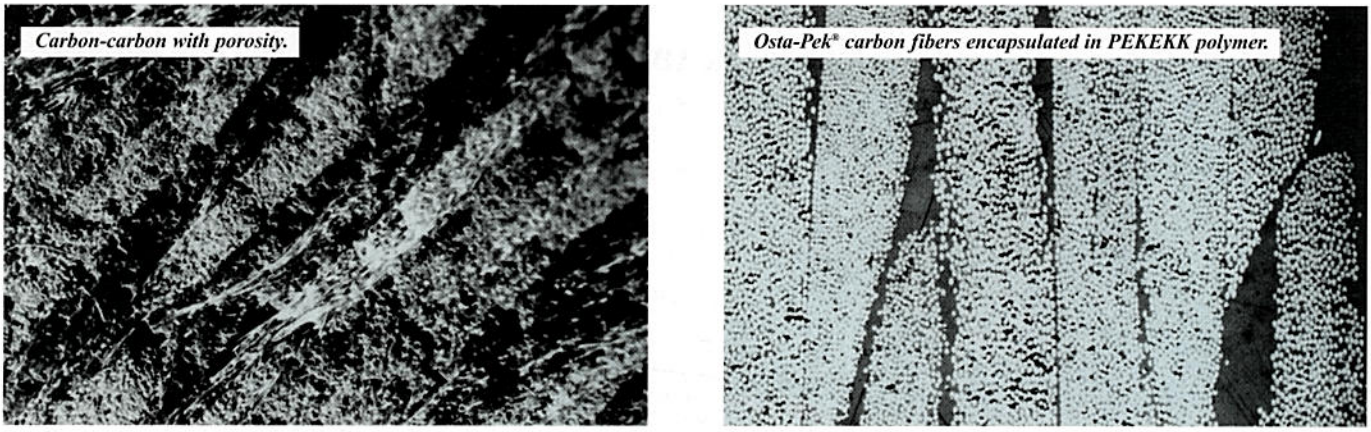

Figure 3 : Carbon-carbon structure compared to the Osta-Pek® composite.

MATERIAL AND METHODS

OSTA-PEK®

Co-Ligne (Zürich, Switzerland) cages for intervertebral fusion are manufactured with a trademark product called Osta-Pek® which is composed of long, continuous carbon fibers encapsulated in the polymer PEKEKK (polyetherketoneetherketoneketone) the orientation of which is controlled *(fig. 2)*. Among the different polymers in the PAEK family (polyaryletherketone), two in particular have been used : PEEK (polyetheretherketone) and PEKEKK, sometimes referred to in the literature under the name Ultra-Pek. Although more difficult to work and less available on the market, PEKEKK in the present case was preferred to PEEK because of its greater physical and chemical resistance properties, which gives it better stability with solvents. It also has better mechanical properties during the molding process *(table 1)*, (8) (9). These characteristics should therefore impart greater stability to the product during a long-term implantation, which is an important requirement for intervertebral fusion cages for which the working life can be up to 40 years. Moreover, some research projects have validated PEKEKK-carbon in an application like the intervertebral cage (10) (11) (12) (13). The company developed an internal process to control the respective content of carbon and PEKEKK as well as the length and orientation of the carbon fibers. This process allows the optimization of the resistance and fatigue characteristics related to the application of intervertebral fusion cages, and more recently to the pedicular fixation system. In addition, the encapsulation of the carbon fibers by the PEKEKK thermoplastic polymer prevents any migration of these fibers (14). Each lot is tested to ensure that there are no voids, which could create points of less resistance within the composite and result in non-uniformity of its mechanical characteristics *(fig. 3)*.

PROPERTIES	PEEK[8]	PEKEKK[9]
Melting temperature, °C	343	381
Glass transition temperature, °C	143	173
Density, g/cm³	1,32	1,3
Fracture load, psi	14,056	15,077
Modulus of elasticity, psi	507,500	580,000
ELONGATION CHARACTERISTICS	**PEEK[8]**	**PEKEKK[9]**
Elastic elongation coefficient, %	5	5,2
Coefficient of elongation at break, %	> 60	> 50

Table 1 : Comparison of the physico-chemical and mechanical properties of PEEK and PEKEKK.

The Techniques

Approach in accordance with regulations

The OSTA-PEK® used to produce interbody cages is implanted in contact with the bone for a duration of more than 30 days. This type of product belongs to class IIb (15), and based on the ISO 10,993-10 standard (16) we performed tests for cytotoxicity, general toxic-

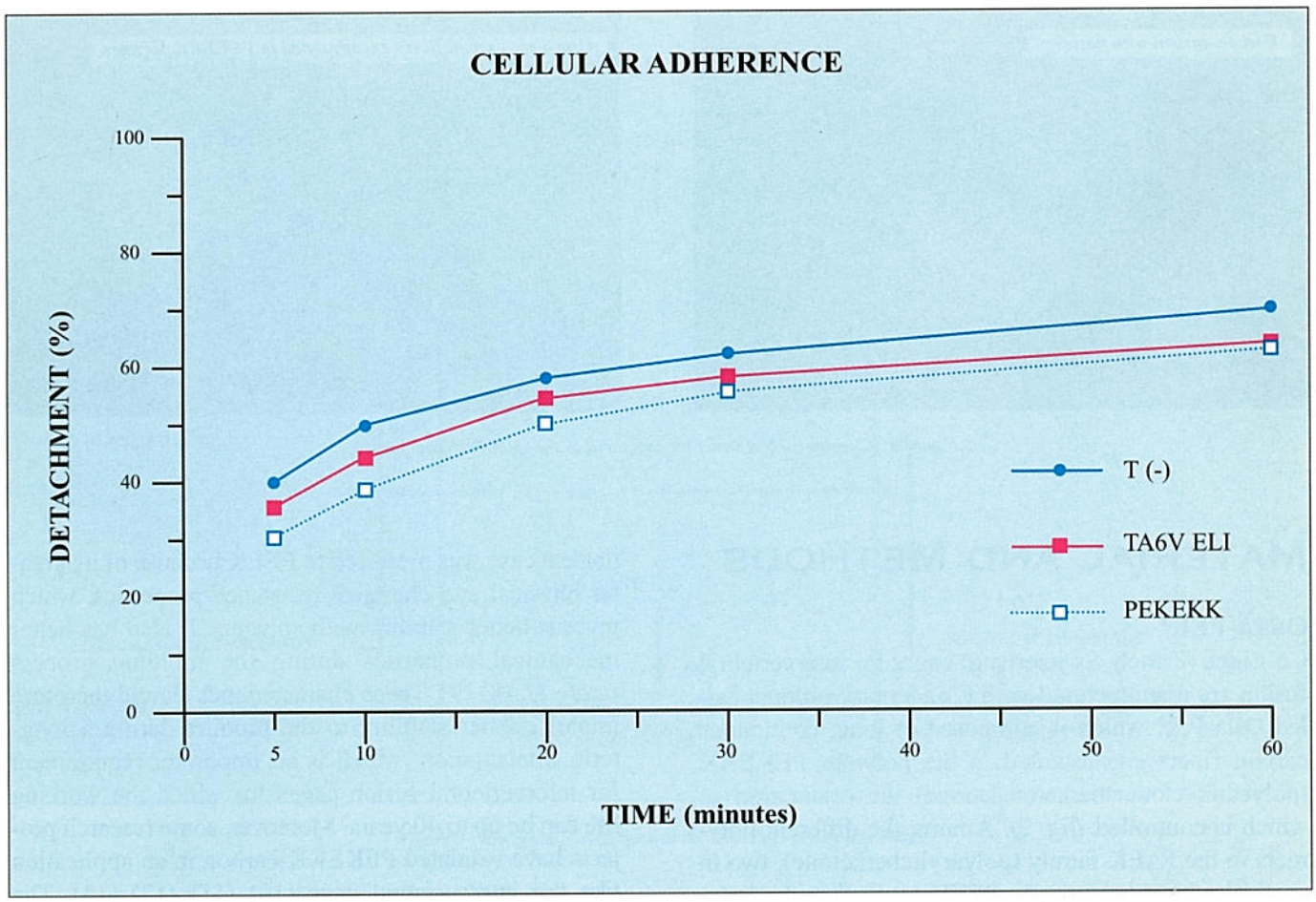

Figure 4 : Graph showing the percentage of cells detached as function of time.

ity, sensitization, genotoxicity (mutagenicity), pyrogenicity and biological load. All of the techniques used are as described in the ISO 10,993 ; EN 30,993 and OCDE standards. The product is used in extract form, and the extraction is done in a 0.9% sterile isotonic solution of ClNa for 120 hours at 37°C at the rate of 5.43 cm^3/ml (17).

Specific Approach

● *In vitro* study.
The behavior of osseous tissue in direct contact with Osta-Pek® was studied using a technique of organotypic culture of human trabecular bone taken from patients aged 10 to 12 years (18). This technique allows the proliferation and adhesion potential of a material to be measured when it is placed in contact with a tissue (19) (20).

● Histological study.
The histological analysis was done on a cage removed after five months of implantation in a 45 year old woman having degenerative spondylosis with spinal stenosis and instability. The implant and the surrounding tissue were removed, fixed in formaldehyde and placed in MMA (methylmethacrylate) after dehydration in alcohol. Slices 120 mm thick are then stained with Stevenel/Picrofuschine Van Gieson blue.

Results

Approach in Accordance with Regulations

In vitro Tests
● Cytotoxicity. The extract and its dilutions showed no cytotoxicity with respect to cells of the L-929 mouse fibroblastic line.

● Mutagenicity. No significant increase in the number of revertants was observed.
● Chromosomic mutations. No clastogenic activity was shown by the in vitro metaphase analysis on human lymphocytes.

In vivo Tests
● Acute general toxicity. The intravenous administration of the extract produced no reaction and no mortality. Autopsy at 14 days revealed no anomaly.
● Sensitization. The extract caused no irritation or allergic reaction in the guinea pig after treatment.
● Pyrogenicity. The sum of the responses of three rabbits did not exceed 1.15 °C. The extract of the product had no hyperthermic effect.
● Biological load. The study was done prior to sterilization, on the packaging and the device, pursuant to the EN 1174 standard. The biological load was determined for aerobic and anaerobic bacteria, yeasts and molds. Only 2.4 colonies were counted for the packaging and 8.4 colonies for the device.

Specific Approach

In vitro Study
The results are summarized in the following table and graph *(table 2 and figure 4)* : the proliferation and adhesion of the osseous tissue are somewhat stimulated in contact with the material.

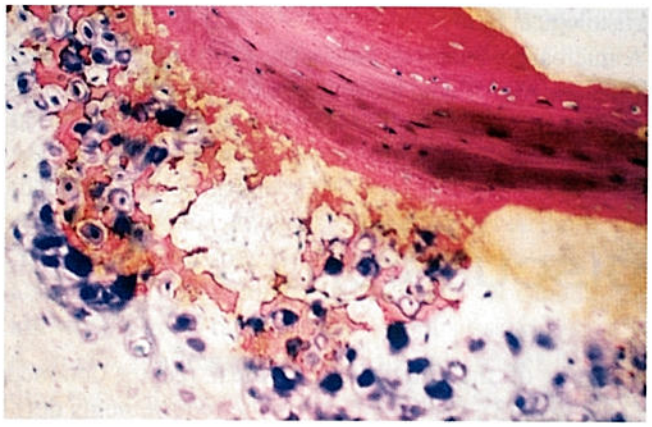

Figure 5 : Microscopic analysis showing the formation of bone and cartilage at the tissue/implant interface (M x 100).

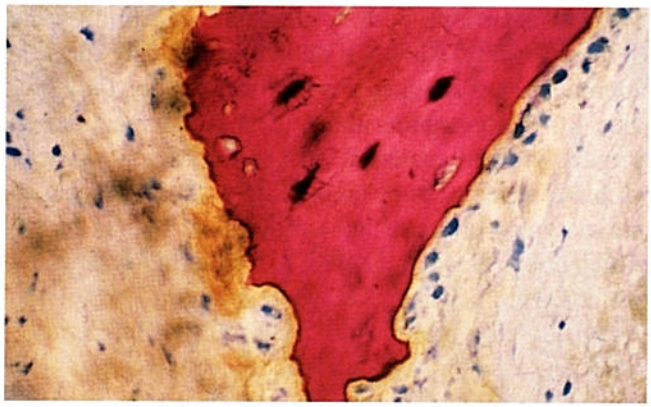

Figure 6 : Microscopic analysis showing the presence of giant cells and particles at the tissue/implant interface (M x 200).

Samples	Migration surface (mm2)	Number of cells per explant	Cellular density (No. cells/mm2)	Viability (% living cells)
T (=)	18,23 ± 3,50	8045 ± 5600	418 ± 260	80 %
TA6V ELI reference	28,45 ± 20,80	6240 ± 2000	264 ± 120	88 %
Osta-Pek® (carbon PEKEKK composite)	23,17 ± 1,75	7393 ± 921	318 ± 15	92 %
T (+) (latex)	3,40 ± 0,82	2443 ± 188	742 ± 234	33 %

Table 2 : Proliferation and migration of human osseous cells cultivated in contact with the Osta-Pek® composite.

Histological Study

A microscopic analysis shows the formation of cartilage and bone *(fig. 5)* with the presence of a few giant cells and particles *(fig. 6)*.

DISCUSSION

Because of the satisfactory clinical results obtained (11) (12) (13), Osta-Pek® meets the requirements defined by the international standards (16), even though implantations in animals have not been performed. However, animal implantation is recommended in order to determine both tissular biocompatibility and biofunctionality. Although clinical studies are the best approach for evaluating this biofunctionality, they provide little information about the tissular reactions in contact with the material. That is the reason we dealt with this aspect first by an in vitro study, employing an organotypic culture technique that uses human tissue, which allowed us to reconstitute a material/osseous tissue interface that is as close as possible to an in vivo interface. The minor stimulation of the proliferation and adhesion of osseous tissue in contact with the material would tend to prove a good integration of this tissue into the Osta-Pek® product. This result seems to be confirmed by the histological analysis of the removed cage, which shows the presence of cartilage and osseous tissue in the vicinity of the implant.

However, this histological analysis has also shown the presence of giant cells and particles around the implant. This observation has often been made by orthopedists who attribute the loosening of a prosthesis to wear of the material and the resultant release of particles (21). Indeed, the phagocytosis of these particles by the macrophages results in their activation and the release of several inflammation mediators (TNF, IL-1, IL-1 ; PGE 2, etc.) which are capable of stimulating osseous resorption (22) (23).

Several studies, and particularly those of T. Glant (24) and Goodman (25) describe the effect of these particles on macrophages in vitro and in vivo. The in vitro approach seemed interesting to us for determining what action the particles deriving from the Osta-Pek® could have on macrophages and on osteoblasts in culture. This preliminary study showed a dose-dependent effect of the particles obtained from the Osta-Pek® both on the growth of human osteoblastic cells as well as on the release of PGE 2 and IL-1 by in vitro human lymphocytes. These results confirm those obtained by Glant with particles of titanium, polymethylmetacrylate and polystyrene. In all cases, this effect only appeared with a strong concentration of particles of 1000 mg/ml (results not published).

Finally, another important question was the origin of these particles. Several hypotheses could explain their presence in the tissues surrounding the implant, with the first and most harmful being wear. The implantation of cages on cadavers has shown the presence of particles around the implant but in smaller quantities *(fig. 7)*, which would tend to prove that they would more likely be generated during polishing than by wear

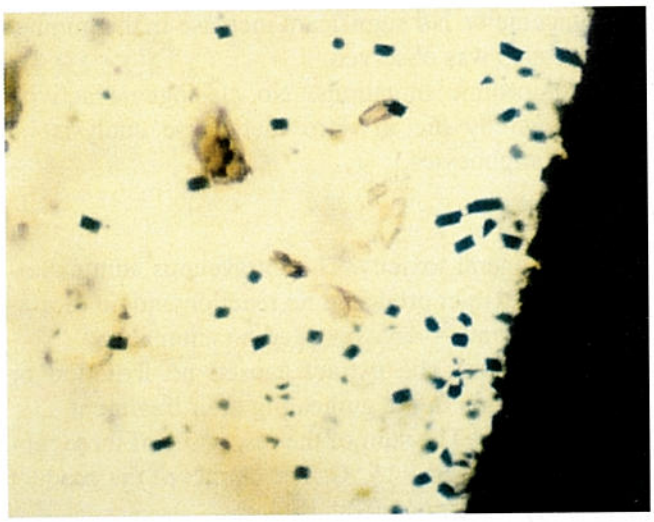

Figure 7 : Microscopic analysis after implantation on cadavers, showing the presence of particles in the vicinity of the implant (M x 10).

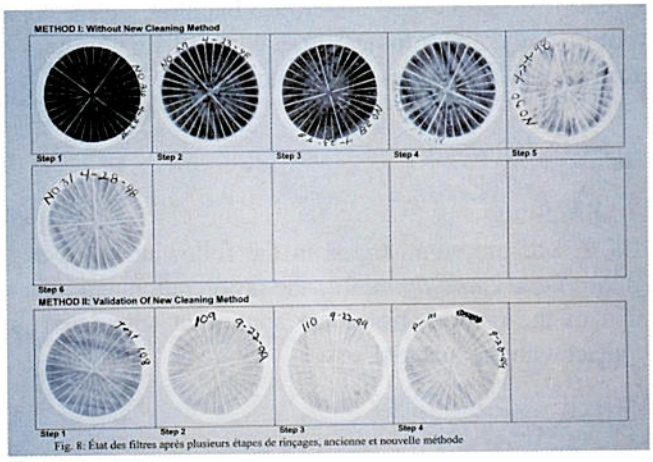

Fig. 8: État des filtres après plusieurs étapes de rinçages, ancienne et nouvelle méthode

Figure 8 : Condition of filters after rinsing, old and new method.

on the implant, which had not been subjected to any movement. Indeed, because the product has a certain porosity, the particles produced by polishing can be trapped in these pores and the usual method of cleaning is not sufficient to eliminate them. A more suitable ultrasound cleaning technique has shown, after filtering the wash solution, a large deposit of particles that decreases and tends to disappear after several washes *(fig. 8)* (results not published).

CONCLUSION

In these studies we have performed on Osta-Pek®, we have attempted to answer the questions that a surgeon must ask about the use of an implant.

- The choice of PEKEKK associated with long, continuous carbon fibers, by using a manufacturing process that can control the quantity of the two components, the length and orientation of the carbon fibers, seems to guarantee good physico-chemical and mechanical performance.
- The biological analysis, which involved both the regulatory and specific approach, shows not only Osta-Pek®'s non-cytotoxicity, but also its capacity to allowing a good rapport with osseous tissue.
- Finally, the improvement of the wash after the product is polished seems to have eliminated the problem of the presence of particles around the implant.

Knowledge of these characteristics is a valuable and indispensable aid to the surgeon when selecting an implant that will perform well for a given application, with the least possible risk to the health of the patient. ■

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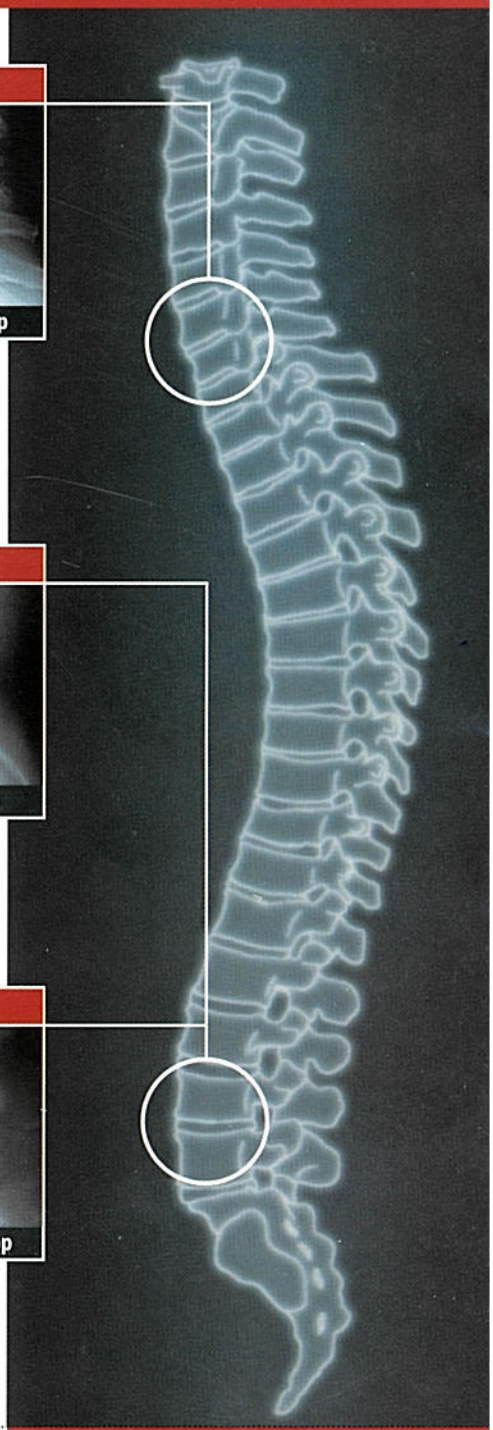

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