Biocoral®

CE 0459

QUESTIONS -ANSWERS

This document is being provided to answers the questions of surgeons and physicians about Biocoral® and its use.

It is based on specific certified scientific studies, various scientific publications and other technical documents.

BIOCORAL FRANCE
Biomaterials & Tissue Engineering Company

Siège Social / Head Quarter :
38, rue Anatole France - 92594 Levallois-Perret Cedex - FRANCE
Tel: + 33 (0)1 47 57 98 43 - Fax: + 33 (0)1 47 57 98 44
e-mail : biocoralfrance@biocoral.com

Production & Services Commerciaux / Manufacturer & Sales Dept.
Le Guernol - B.P. 26 - 56920 Saint Gonnéry - FRANCE
Tél : + 33 (0) 2 97 38 40 88 - Fax : + 33 (0) 2 97 38 41 13
e-mail : info@biocoral.com
www.biocoral.com

G MED
ISO 13485

SUMMARY

I - GENERAL REMARKS AND THE ROLE OF BIOCORAL®

II - CHARACTERISTICS OF BIOCORAL®

III - HOW TO USE BIOCORAL®

IV - RECOMMENDATIONS WHEN USING BIOCORAL®

V - BEHAVIOR OF BIOCORAL® AFTER IMPLANTATION

VI - BIOCORAL® RADIOLOGICAL VISUALIZATION AND ITS EVOLUTION

VII - STRICT CONTRA-INDICATIONS

VIII – THE CONFORMITIES WITH THE EUROPEAN AND INTERNATIONAL NORMS

IX – REFERENCE

I - GENERAL REMARKS AND THE ROLE OF BIOCORAL®

1. What is Biocoral®?

Biocoral® is the only natural bone substitute wholly mineral composed of calcium carbonate (>98%), obtained from the natural coral exosquelette.

2. What is innovative about Biocoral®?

Once implanted in bone tissue, Biocoral® is gradually resorbed and simultaneously replaced by newly formed bone. This destruction - reconstruction process is identical to the physiological skeleton normal bone process.
The new bone formed has the same characteristics (physical, chemical and mechanical properties) than the recipient bone. Biocoral® allows a return to the initial pre-pathological state.

3. For how long has Biocoral® been studied experimentally and clinically?

• The first experimental studies of Biocoral® began in 1977, at the Orthopedic Research Institute at GARCHES - FRANCE.
• The first clinical studies in human subjects were carried out in 1979, at the Raymond-Poincaré Hospital at Garches - FRANCE. in Pr Robert. Judet's orthopaedic department.
• Since numerous experimental and clinical studies were conducted by various civil, military hospitals and university hospital center confirming the advantage of Biocoral®.

4. How extensive are the experimental studies devoted to Biocoral®?

Tests have been carried out since 1977, according to international standards, in order to study the biocompatibility and biological function of Biocoral®. Since, more than 500 000 Biocoral® implantations were performed and compared with bone autografts, controls without implants, and implantations of other materials, such as hydroxyapatite or tricalcium phosphate.
These studies, conducted in vivo, examined not only biocompatibility but also the role of coral and the basic processes governing its fate in bone tissue. They have also contributed to the definition of the requirements for transformation of natural coral to Biocoral®.

5. How extensive are the clinical studies of Biocoral® conducted in human subjects?

Thousands of human applications have been monitored between 1979 and 2006, in orthopedic surgery, neurosurgery, plastic surgery, dental surgery and Cranio-Maxillo-Facial surgery.

These applications have provided a basis for definition of Biocoral® indications and have shown that the experimentally-observed behavior of Biocoral® is reproduced in human subjects.
The last prospective and randomized study (concerning 120 patients) was performed in 14 European University Hospitals civil and militaries between 2000 and 2005. This study has been initiated after various retrospective studies conducted between 1990 and 1997 covering more than 55 patients. That study enhanced the interest of Biocoral® in the treatment of osteoporotic unstable femoral neck fractures.

6. Is Biocoral® bioactive?

Yes. Since it induces a specific biological activity-in the recipient bone-similar to the normal bone metabolism. The Biocoral® has a behavior autologous bone graft-like, under specific conditions well defined to day.
Yes, because it induces a specific biological activity identical to that of the recipient bone metabolism. Biocoral® behaves as a true auto-graft of course in condition that it should be stabilized.

7. Is Biocoral® bioresorbable?

Yes. It has been demonstrated that Biocoral® implanted in bone is gradually resorbed, through the action of carbonic anhydrase present in the osteoclasts. This resorption represents one stage in the process of bone restoration.

8. Is Biocoral® an osteoconductive material?

Yes. A material is known as to be osteoconductive when it allows its penetration through pores, conducts or by appropriate cells (bone marrow) and its transformation in newly formed bone.
The experiments in animal models and clinical human trails have shown that Biocoral® is an osteoconductive substance due to its open porosity.

9. Is Biocoral® osteophilic?

Yes. Experiments have demonstrated prompt formation of bone adjacent to the Biocoral® implant directly in contact and simultaneously in the core of the biomaterial. These experiments have also shown that Biocoral® attracts osteogenic cells (osteoclast and osteoblast) and enhances bone neoformation. Histologically, there is no fibrous tissue formation at the interface between the mineral matrix and the newly formed bone.

10. Is Biocoral® osteoconductor?

The international scientific community has yet to reach a consensus regarding the definition of bone induction.
Biocoral® is not osteoinductor: when implanted in non osteogenic tissu such as muscle, fibrous tissu, etc.)
Besides, due to its biocompatibility and resorbability, Biocoral® induces a bone neoformation when implanted in bone tissu.

11. In which kind of animals' species has Biocoral® been tested?

Biocoral was implanted with success in rats, rabbits, dogs, sheeps and pigs. Many others studies are continuing in some of these species, as well as in monkeys.
Clinical trials have been performed in veterinary clinics on birds, dogs and cats.

12. Can all kind of coral species be used?

No. Only three of the 2500 listed corals species meet the requirements of bone surgery. They are selected Porites, Acropora and Lobophylia. Those species have been selected on the basis of specific experiments in animal models and clinical applications in humans.
The animal experiments and the clinical applications allow a targeted adaptation of the selected corals to the specific indications.

13. Do any synthetic biomaterials exhibit the similar properties than Biocoral®?

No. Although it is possible to produce a replica of the architecture of the coral skeleton by industrial thermochemical transformation of calcium carbonate into calcium phosphate, the obtained material (hydroxyapatite) loses its capacity of resorption, all its useful mechanical properties and the new bone can not be formed.
The name of «coral» used sometimes to describe the surface component of some cimentless prosthetic device is incorrect. In fact, this surface component is hydroxyapatite, which acts as to fix the device in the bone. This «so-called» coral is very slowly restorable, is laid in a very thin layer by a plasma torch on the prosthetic device surface and has no mechanical keeping.

14. Do any synthetic bioceramics exhibit the similar properties than Biocoral®?

There are many ceramics with biological applications, including hydroxyapatites, tricalcium phosphates, aluminas, zircons, bioglasses, titanium nitrides and carbides, etc. All of the above mentioned products are synthetically manufactured.
Biocoral® is the only natural porous biological ceramic wholly mineral.
• Biocoral® bioactivity, together with its osteoconductive and osteophilic properties, induces specific biological activity in the recipient bone similar to the physiological natural bone metabolism. This activity leads to graduate resorption of Biocoral® by osteoclasts and its replacement by osteoblasts in newly-formed bone,
• Biocoral® architecture is propitious to bone ingrowths. Its characteristic features include an open porosity (all the pores communicate between them), the volume, the size, the thickness of the porous walls and structural regularity of pores. These characteristics allow a blood cells circulation and a penetration in the core of the graft by bone marrow cells (blood, anions, cations, etc…). Furthermore, Biocoral® exhibits remarkable qualities of mechanical resistance even when porosity volume approximates 50%. It is similar to those of the

cancellous bone when mechanical strains act in compression but it's mechanical resistance in flexion and in torsion is weak,

• Biocoral® chemical composition as a calcium salt (Calcium Carbonate >98%) and crystallographic nature (aragonite) complete its physical properties by allowing, thanks to its bio-resorbability, the process of resorption-remineralization by newly bone formation.

Conversely, the, transformation (by heating) of aragonite into calcite or hydroxyapatite (ceramic industrial process) would delay significatively the physiological process.

15. Is it possible to compare Biocoral® with autologous bone grafts?

Yes. Bone autografts are evidently the best available biomaterial for use over the entire range of indications. However, the reasons described below encourage us to use Biocoral® as bone substitute.

Despite their numerous advantages, bone autografts are not free from drawbacks:

• Surgery is necessary at different sites other than the main treatment site,
• Bone removal may involve blood loss that may require blood transfusion, a procedure best avoided because of the risk of contamination by pathogens HIV, Hepatitis, etc.,
• Surgery procedure is systematically prolonged,
• Important pains at the graft donor site (of iliac crest) are felt by the patient,
• In the event of repeated surgery, the amount of bone available may be inadequate,
• One or several scarring occurs at the site of the curative surgical procedure which is the visible undesirable consequences of using autograft.
• In some plastic surgery indications, autografts may be resorbed before replacement is sufficiently advanced to ensure the desired result.

Because of the reason mentioned above the surgeon may decide to use Biocoral® as a bone substitute.

Biocoral®, the only natural wholly mineral bone substitute, correspond to these qualities requirements Biocoral® is an asset for the physician:

• Biocoral® allows a return to the prepathological state due to the process of resorption and replacement by the osteoinductive cells of the recipient bone,
• When Biocoral® is presented in the form of block, despite the absence of malleability, it can be adapted to the recipient site by using a set with diamonds grinding stone or a disc,
• Biocoral® is highly malleable when used in the form of granules or beads. These round shapes allows Biocoral® to fulfill all types of cavities, cortical bone and periosteum interface etc,.
• Moreover, the different pore volumes found in the three natural corals species offer a large array of possibilities according to:
    - the mechanical strains imposed by certain surgical indications,
    - the desired rate of the resorption-replacement process,
• Many basic researches are conducted to quantify the Biocoral® resorption time and/or that of biomaterials close to the natural coral depending on the number of osteoformatric cells and/or bone osteogenic factors such as BMP.

• Biocoral® is a useful adjunct to auto grafting since it can, if necessary, be used to fill the cavity created by graft removal (iliac crest), thus alleviating post-operative pain at the graft donor site by mechanical stabilization and ensuring restoration of bone reserves and maintenance of plastic integrity.

II – CHARACTERISTICS OF BIOCORAL®

16. What are the requirements for obtaining a biomaterial from natural corals?

Raw corals can be used as a surgical biomaterial only after the following steps according to the international good practices:

- Selection of coral species on the basis of their architectural and physico-chemical properties,
- Strict harvesting conditions,
- Precise characterizations,
  - Chemical,
  - Physical,
  - Mechanical.
- Use of strict protocols for:
  - Preparation,
  - Purification,
  - Shaping techniques,
  - Sterilization,
- Routine checks:
  - Chemical,
  - Physical,
  - Sterilization,
- Permanent quality control by the laboratory responsible for the compliance with prestablished standards.
  - Traceability conforms to the international standards.

17. What is the chemical composition of Biocoral®?

Following the last studies of Pr Le Petitcorps in 2006 at CHU Bordeaux, L'ICMCB-ENSCPB (one of the CNRS laboratories (UPR 9048)), Biocoral®'s chemical composition is confimred being wholly mineral as described below:

- Calcium Carbonate ……..>98%
  (including calcium >40 %)
- Oligo- elements …… …. 0,7 and 1%
  (including fluor and strontium)
- Magnesium ……..……. .0,05 and 0,2%
- Sodium .....……..<1%
- Potassium ……....<0,03%
- Phosphorus in the form of phosphates ……...<0,05%
- Water ……..<0,5%

Strontium is highly important in the stability of Biocoral®'s aragonite and plays an important role in the formation and growth of the bone crystal. It has a protecting action on the calcification mechanism and increases the bone mineralization.

Several components are present at levels equivalent to those found in mammalian bone, notably trace elements like fluor, which play a vital role in the process of mineralization and in the activation of enzymatic reactions in bone cells.

ALL OF THE MENTIONED ELEMENTS ABOVE CONFIRM THAT BIOCORAL® IS THE ONLY NATURAL WHOLLY MINERAL BONE SUBSTITUTE.

18. Does the organic component of Biocoral® result in risks of specific intolerance?

No. The methods of purification allow the elimination of all organic trace. Biocoral® is the only natural wholly mineral product. Lack of proteins delete all immunological reactions.

19. What is the architectural organization of Biocoral®?

Biocoral®'s architecture is entirely porous, and is defined by the total volume, interconnection and organization of pores.
Bone cells can freely invade the open porous structure of Biocoral® and deep in its core by the cells of bone marrow, blood of the recipient bone. This cellular invasion determines the first phase of the bone restoration process characterized by the development of a neo-vascularization.
Some corals (Porites in particular) bear a striking architectural resemblance to the cancellous bone.

20. What is the porosity volume of Biocoral®?

Biocoral®, due to its porosity (50% and 20%) which is similar to cancellous bone and cortical bone respectively, has specific mechanical resistance qualities in compression.
Acropora 20% of porosity is very close to the cortical bone. The Porites 50% of porosity is very close to the spongious bone. That porosity allows the surgeon to choose Biocoral®, according to the clinical indication. However, those specifications do not constitute a rigid standard. Biocoral® (natural calcium carbonates) with different porosities can be used according to the operating procedure.

21. What is the pore size of Biocoral®?

From 150 to 500 microns, depending on the species, selected according to clinical indications. It has previously been shown that these sizes are optimal for occupation by fluids and bone marrow cells in order to complete mineralized neoformed bone. For indications where dense material is necessary, for example for strong mechanical compression strains, the microporous or non porous natural calcium carbonates can be used.

22. Are Biocoral® mechanical resistance properties satisfactory?

The mechanical properties of Biocoral®, tested by compression, are identically similar to the bone structure. For Biocoral® with 50% porosity, the values of the breaking compression stress and modulus of elasticity fall between those of cortical bone and cancellous bone. Conversely, it must be kept in mind that the torsion or flexion strains are very low whatever the coral species.
Mechanical compression strength increases as porosity decreases.
Thus Biocoral® with 20% porosity offer the mechanical properties similar to those of cortical bone, and microporous or even dense Biocoral® offer mechanical compression properties greatly superior to those of fresh healthy bone.

23. Does Biocoral® become friable, once being impregnated with physiological or other fluid?

No. The growth of coral in a marine environment protects it from early or delayed dissolution and friability.
The mechanical properties of Biocoral® are unaltered in the presence of fluids except when H^+ ions induced by part of the osteoclasts membrane are in close contact with the bony structure (first step of demineralization).

24. What is the sterilization procedure used for Biocoral®?

Radiosterilization is obtained byβ. Rays. The delivery dose is 25 KGrays.

25. Does radiosterilization alter the chemical, physical or mechanical properties of Biocoral®?

No. The tests performed on samples sterilized by ionizing radiations have not revealed any chemical, physical or mechanical alteration in the Biocoral® properties.

26. What is the shelf life of Biocoral®?

Five years from the date of sterilization.

27. In what forms are Biocoral® available?

- Granules, Beads, Blocks,
- Shaped standard prostheses or specific design according to the surgeon's will.

III - HOW TO USE BIOCORAL®

28. Can Biocoral® be resterilized?

No, unless end-users possess radiosterilization equipment.
No. The sterilization is reserved to the professionals in the sterilization field. The users do not have the adequate means of radiosterilisation.
In addition, it is recommended not to use the resterlization by heat as the aragonite is transformed into calcite from a certain temperature. Biocoral® will face the physicochemical changes which will prevent it from being resorbable, its replacement by newly bone formed and its mechanical properties would be significatively reduced.

29. At what temperature should Biocoral® be conserved?

No particular storage conditions are necessary for Biocoral®.
Refrigeration is not necessary.
Biocoral® can be stored at room temperature (15°C-40°C or 60°F-100°F).

30. Can Biocoral® be remodeled during surgery?

Yes. Nevertheless, the complete remodeling of the Biocoral® may alter its mechanical properties by inducing microfractures undetectable with the naked eye. Adaptation of shapes and sizes should only be performed using diamond-edged cutting or drilling instruments.
The use of other instruments may contaminate Biocoral® with metal particles or other foreign bodies.

31. Can "in situ" drilling be used to attach Biocoral®?

Yes, but there is an important risk of induced fractures. The use of preperforated blocs of Biocoral® is therefore highly recommended.

32. Is special preliminary treatment of recipient bone surfaces necessary?

As for autografts, recipient bone surfaces should be cleaned up. In case of bone cavities, if the peripheric membrane becomes ossified, recommendation is to open the membrane in order to allow blood and bone marrow cells invasion. The surgical process is identical in a non-union fracture. The medullary canal must be open on each side of the fracture site.

33. What method of osteosynthesis should be used to maintain Biocoral®?

There is no specific **osteosynthesis** to maintain Biocoral®; the surgeon may chose the method generally practiced for implantation of autografts. The **osteosynthesis** must be stable as for a bone auto-graft. **Osteosynthesis** can be removed, if necessary, as soon as consolidation occurs, according to the classical orthopedic rules. It can be performed even before complete visual radiological disappearance of Biocoral®.

34. Should Biocoral® be impregnated with blood before implantation?

Yes. This is recommended, particularly when it is necessary to obtain immediate cohesion between Biocoral® granules or beads. Once Biocoral® is mixed with bone marrow or blood, the presence of the Fibrin, facilitate its use and application into the surgical recipient bone.

35. Is it desirable to impregnate Biocoral® with bone marrow?

Yes. This is almost recommended to do it in particular in traumatologic surgery.

36. How can bone marrow be taken off?

The method is identical to those of any bone marrows swab. The preference site is the iliac crest with a Mallarme's trocar, 3cc to 5cc of bone marrow are taken off in each sample site. The surgeon mixed the bone marrow with Biocoral® which absorbed them immediately due to its ideal porosity.

37. Should Biocoral® be mixed with autografts?

The reason for using Biocoral® is to avoid the use of autografts once needed. Obviously, if chips or fragments are available, they can and must be used in combination with Biocoral®. Though it is not obligatory but it is highly recommended.

38. Is it preferable to implant small fragments of Biocoral® at the recipient sites rather than a single larger piece?

There is a strict rule, whatever clinical indications. The surgeon must choose the shape which gives the largest *surface area in contact* with the recipient site.

Nonetheless, the following three situations can be considered:

• Filling: if there are few or none mechanical strains small fragments can be used (beads, granules, sticks, etc.),
• Interposition: The use of a single block is recommended because it's good mechanical resistance. The good quality of the fixation will avoids displacement of the single block,
• Apposition: The choice will depend on the planned method of retention, and on the configuration of the recipient site, "in-lay or on-lay" according to the recommendations for Biocoral®'s use.

39. What is the maximum size of a Biocoral® implant, beyond which function is compromised?

The maximum size of a Biocoral® implant depends to the condition of the recipient bone and on the maximum size of the contact between Biocoral® and bone. There is, therefore, no absolute value. In this case, it should be taken in consideration the rule «the largest surface area in contact» and the necessity to impregnate Biocoral® with bone marrow.

However, the indication should, be carefully discussed. The association of any growth factors may be considerate.

IV-RECOMMENDATIONS WHEN USING BIOCORAL®

40. Biocoral® preparation before its placement in the bone site,

It is recommended to impregnate Biocoral® with bone marrow in particular in traumatology. Biocoral® can also be impregnated with blood, growth factors biological sterile fluid and antibiotics.

41. Biocoral® placement in the recipient bone,

Biocoral® placement and its contention must be rigorously executed according to the following steps:

• The placement is executed by smooth manual impaction. It is necessary to avoid striking Biocoral® with metal instruments in order to avoid fracturing the implant,

• The retention is executed by metallic osteosynthesis. The stabilization must be the same as for the bone graft.

Mobility of Biocoral® may generate an inflammatory reaction followed by either discharge of sterile fluid or local fibrous encapsulation caused exclusively by mechanical bone friction. No immunological phenomenon of rejection was described and/or highlighted in scientific way.

42. The contact of Biocoral® with metal,

Biocoral® coexists perfectly with all non-oxidable metals. Nonetheless, friction between Biocoral® and metal may cause surface erosion, and release metal particles which may lead to inflammation responsible of metallose.

However, these facts were not reported to date. Within the framework of the posterior vertebral arthrodesis, the contact with the metal of the stems never determined this type of reaction.

V - BEHAVIOR OF BIOCORAL® AFTER ITS IMPLANTATION

43. Does the implantation of Biocoral® in non-osseous tissue cause intolerance or rejection?

Biocoral® has been implanted in tissues other than bone, including:

- Subcutaneous,
- Intramuscular,
- Perivascular,
- Perinervous,
- Palatine fibromucous tissues.

No short, medium or long term reactions of intolerance, rejection or encapsulation have been noted.

44. Does implantation of Biocoral® in non-osseous sites induce anarchic calcification?

No anarchic calcification has been noted in any of the soft tissue implanted sites. The small fragments are even resorbed.

45. What happens at the bone- Biocoral® interface?

Bone neoformation occurs directly at the bone Biocoral® interface, without fibrous tissue interposition

46. What is the volume available for absorption of physiological fluids immediately after Biocoral® implantation?

The total pore volume, if Biocoral® has not been mixed with bone marrow. On average, approximately 5cc of bone marrow fulfill 6cc of Biocoral® beads.

47. What is the time of invasion by the osteogenic cells?

Immediately after Biocoral® implantation.

48. What is the process of Biocoral® resorption?

Resorption may involve more or less complex physiological processes. It has been shown that resorption of the carbonate skeleton of Biocoral® is at least partly due to the action of an osteoclast carbonic anhydrase.

49. How long do resorption and bone neoformation take?

These processes begin immediately after Biocoral® implantation and will continue in time depending on:

- The volume of Biocoral®,
- The porosity of Biocoral®,
- The implantation site,
- The general condition and age of the patient, (osteogenic cells),
- Strolling around (perimeter of walk, rhythm step and mobility).

These items are in direct relation with the vascularization.Consolidation is achieved within a period comparable to that noted with autografts, and in any case long time before Biocoral® radiological disappearance. This effect may require several months, or even years, depending on the criteria as described above.

50. What are the characteristics of the neoformed bone after remodeling?

Studies of the histology, architecture, chemistry, microstructure and crystallography of neoformed bone all show that once repair is achieved the remodeled bone is in all ways similar to the recipient bone.

51. Is there a difference in Biocoral® behavior after its implantation in flat or in long bones?

No. However, the rate of remodeling does differ between these two types of bone. It is slower in membrane bone than in enchondral bone. Consequently, the process of neoformation and apposition are different, but the behavior is identical in both cases. To obtain identical resorption, it is necessary to add growth factors in a membrane bone.

52. Are there post-operative events specific to Biocoral®?

No. The immediate and long-term postoperative courses are identical to those seen with an autologous bone graft.

53. Can signs suggesting the intolerance of Biocoral® occur?

No. None instance of intolerance and allergic reaction were seen during Biocoral® immunogenicity tests.
In some cases of mobile implants, local erythema, and even edema have been noted, suggesting rejection of the graft over variable periods (15 days to 3 months).
However, in some cases of Biocoral®.mobility, it has been observed a local reaction with redness, edema, which could suggest in different time (between 15 days to 2 months) an implant removal. It is related to secondary reaction due to a mechanical irritation, following trauma or inopportune manipulation (for example implant fractures). In some of these rare cases it is necessary to remove the implant.

54. What is Biocoral® behavior when it is implanted in septic conditions or if an infection occurs after surgery?

• In the event of proven infection or of imperfectly drained old infection, the process of resorption-replacement is impaired. Biocoral® remain identical in its state at the time of its implantation. It is contra-indicated to execute such a graft. At our knowledge, Biocoral® has never been used with the Papineau's method.
• In the event of post-operative secondary infection, the behavior of Biocoral® depends on the time of onset of infection:
- If the resorption-replacement process is established, Biocoral® will remain integrated into the recipient bone,
- Otherwise, Biocoral® undergoes no change.
The therapeutic approach will depend on these data. If suppuration is superficial and amenable by antibiotic therapy, there is no need to remove the implant. In the opposite, if the infected site requires surgical cleansing, removal of the implant is necessary, as with any autologous, hetero or allograft.

55. What is the effect of eventual radiotherapy and/or chemotherapy on Biocoral®?

The clinical observations in human have shown that radiation therapy and/or chemotherapy do not have any secondary effects on Biocoral® and do not alter the kinetic process and the conduct of Biocoral®.

VI - BIOCORAL® RADIOLOGICAL VISUALIZATION AND ITS EVOLUTION

56. Is Biocoral® visible on radiographs?

Yes, its mineral density makes it radio-opaque, giving a more contrasted image than that of cancellous or cortical bone.

57. What is Biocoral® radiological evolution?

Biocoral® disappears completely and is simultaneously replaced by neoformed bone.
The none systematically of a linear density surrounding, blurring of contours, shrinkage of volumes, and decreases in radiodensity is also signs of Biocoral® resorption.
All these signs are time-dependent and variable in amplitude. They depend on individual metabolisms, on the volume of the Biocoral® and on the clinical circumstances.
A large fragment of Biocoral® may be visible for years without compromising the physiological and mechanical qualities of the result.

58. What is the histological significance of the peripheral linear density quite often seen at the bone-Biocoral® junction?

This is the zone of complete resorption of Biocoral® which is being replaced by osteoid connective tissue.
This tissue is undergoing mineralization and is not yet radio-opaque.

59. For how long does Biocoral® remain visible on radiographs?

Biocoral® is visible for several months or even several years before complete disappearance occurs.
Nonetheless, consolidation is generally achieved long time before, as shown by cortical bone repairs.

VII – STRICT CONTRA-INDICATIONS

60. Are there any contra-indications when using Biocoral®?

Yes, there are several cases in which Biocoral® must not be used such as:

- Patent or imperfectly drained osteomyelitis,
- Necrosed or necrotic recipient site,
- Intra-articular implantation,
- Biocoral®, because of its mineral composition will definitely damage the soft tissue (ligaments, cartilage, and meniscus).

VIII – THE CONFORMITIES WITH THE EUROPEAN AND INTERNATIONAL NORMS

61. Biocoral® conformities with the European and International norms.

Biocoral® although marketed since the end of the years 80, was the first bone substitute registered in France with TIPS (Tarifs Interministériels des Prestation Sanitaires). Nevertheless within the framework of its registration, Biocoral® has been received approving opinion of Microbiological Committee of Health on July 05, 1995 referanced under the number 9600201B01.

Biocoral® received the authorization of marketing in the European countries market "EC lable" on December 30, 1996. Since, this authorization has been renewed several times and it is into force currently.

Biocoral® manufacture facility complies with ISO 13485 version 2003 which allow the Company to continue to market its products in CANADA.

IX – REFERENCES BIBLIOGRAPHICS

IX.1. FUNDAMENTAL RESEARCH

PETITE H.P., VIATEAU V., GUILLEMIN G. *(LRO-CNRS, Université Diderot, Paris, FRANCE)*
Tissue-engineered bone regeneration
Nature Biotechnology, 2000; 18: 959-963

DUBRUILLE JH. *(Université de Paris VI, FRANCE)*
Evaluation of combinations of Titanium, Zirconia, and Alumina Implants with 2 Bone Fillers in the Dog.
Int. J. Oral&Maxillofacial Implants, 1999;14:271-277

GAO T.J, TUOMINEN T.K., LINDHOLM T.S., KOMMONEN B., LINDHOLM T.C.
(University of Tampere and Helsinki, FINLAND)
Morphological and biomechanical difference in healing in segmental tibial defects implanted with Biocoral® or tricalcium phosphate cylinders.
Biomaterials, Elsevier Science Limited., 1997; 18: 219-223,

FUJIMORI Y., SUGAYA K.,IZUMI H., KOZAWA Y.*(Nihon University, Matsudo, Chiba, JAPAN)*
Scanning Electron Microscopic observation of Bone Marrow-derived Osteoclast-like cells resorbing Coral.
J. Oral Biol., 1997; 39: 241-246

REIS S.A., VOIGT C., MULLER-MAI C. *(Free University of Berlin, GERMANY)*
Procollagen α1 (I) transcripts in cells near the interface of coralline implants in rats, detected by in situ hybridization
Clin Oral Impl Res, 1996; 7: 253-260

MOON I.S., CHAI J.K., CHO K.S., WIKESJÖ U., KIM C.K.
(Yonsei University, Seoul, KOREA)
Effects of polyglactin mesh combined with resorbable calcium carbonate or replamineform hydroxyapatite on periodontal repair in dogs.
J. Clin. Periodontal, 1996; 23: 945-951

BRAYE F., IRIGARAY J.L., JALLOT E., OUDADESSE H., WEBER G., DESCHAMPS N., DESCHAMPS C., FRAYSSINET P., TOURENNE P., TIXIER H., TERVER., LEFAIVRE J., AMIRABADI A. *(CNRS de Clermont-Ferrand et Université Blaise Pascal, Aubière, FRANCE)*
Resorption kinetics of osseous substitute : natural coral and synthetic hydroxyapatite.
Biomaterials, Elsevier Science Limited., 1996; 17 (n°13): 1345 - 1350.

IRIGARAY J.L., OUDADESSE H., SAUVAGE T., BLONDIAUX G.
(CNRS de Clermont-Ferrand et Université Blaise Pascal, Aubière, FRANCE)
Mesure de la cinétique de transformation d'un Biocoral implanté dans les fémurs de mini-porcs par des méthodes nucléaires d'analyse.
Actualités en biomatériaux, Edition Romillat, 1996; 3: 287 - 291.

IRIGARAY J.L., BRAYE F., OUDADESSE H., JALLOT E., WEBER G., AMIRABADI A., TIXIER H. *(CNRS de Clermont-Ferrand et Université Blaise Pascal, Aubière, FRANCE)*
Diffusion of mineral elements evaluated by PIXE at the bone-coral interface.
J. Biomater. Sci Polymer Edn, 1996; 7 (n°8): 741 – 749.

MULLER-MAI C., VOIGT C., GROSS U.M. *(Free University of Berlin, GERMANY)*
Substitution of natural coral by cortical bone and bone marrow in the rat femur. Part II Sem, Tem and in situ hybridisation.
Journal of Materials Science : Materials in Medicine, 1996; 7: 479 - 488.

ARNAUD E., MORIEUX C., WYBIER M., de VERNEJOUL M.C.
(Hôpital Necker, Paris, FRANCE)
Etude d'un substitut osseux avec TGF-β1, colle fibrinogénique et corail.
Actualités en biomatériaux, Edition Romillat, 1996; 3: 277 - 283

GROSS U., VOIGT C., MULLER-MAI *(Free University of Berlin, GERMANY)*
Cellular responses and mineralisation after implantation of natural coral in trabecular bone.
Bulletin de l'Institut Océanographique, Monaco, n° spécial 14, 3, 1995

SUGAYA K., KOZAWA Y., IZUMI H.*(Nihon University, at Matsudo, Chiba, JAPAN)*
The ultrastructural study of the subcutaneous and the tooth extracted cavity implants of the coral
Bulletin de l'Institut Océanographique, Monaco, n° spécial 14, 3, 1995

GUILLEMIN G., HUNTER S.J., GAY C.V.
(LRO, Faculté de médecine Lariboisière, Paris, FRANCE)
Resorption of natural calcium carbonate by avian osteoclasts in vitro.
Cells and Materials, Vol 5, N° 2, Pages 157 - 165, 1995.

IRIGARAY J.L, OUDADESSE H., SAUVAGE R., EL FADL H., BLONDIAUX G.,
LEFAIVRE J., BARLET J.P., TERVER S., TIXIER H.
(CNRS de Clermont-Ferrand et Université Blaise Pascal, Aubière, FRANCE)
Comparison of the ossification kinetics after implantation of a radioactivated coral and a natural coral.
Journal of Materials Science : Materials in Medicine 6 (1995) 230-234.

PETITE H.P., CHRISTEL P.S., TRIFFITT J.T. *(L.R.O. -CNRS, Paris, FRANCE)*
Tridacna is a suitable material for human bone marrow cell growth
Bulletin de l'Institut Océnographique, Numéro spécial 14,3 - 1995.

BOUCHON C., LEBRUN T., ROUVILLAIN J.L., ROUDIER M.
(Université Antilles-Guyane, FRANCE)
The Caribbean scleractinian corals used for surgical implants.
Bulletin de l'Institut Océnographique, Numéro spécial 14,3 - 1995.

ARNAUD E., MORIEUX C., WYBIER M., de VERNEJOUL M.C. *(Hôpital Necker, Paris, FRANCE)*
Potentiation of Transforming Growth Factor (TGF-Beta 1) by natural Coral and Fibrin in a Rabbit Cranioplasty Model.
Calcified Tissue International, 54:493:498, 1994.

ARNAUD E., MORIEUX C., WYBIER M., de VERNEJOUL M.C.
(Hôpital Necker, Paris, FRANCE)
Ostéogenèse induite par l'association de facteur de croissance, de colle fibrinogénique et de carbonate de calcium.
Annales de Chirurgie Plastique, 39, 4, 491 - 498, 1994.

DAMIEN C.J., RICCI J.L., CHRISTEL P., ALEXANDER H., PATAT J.L.
(Intermedics Orthopeadics, Denver, USA / LRO, Paris, FRANCE / Hospital for joint disease, New-York, USA)
Formation of a calcium phosphate . Rich layer on absorbable calcium carbonate bone graft substitutes.
Calcified Tissue International 1994; 55: 151-158

VOIGT C., MERLE C., MULLER-MAI C., GROSS U. *(Free University of Berlin, GERMANY)*
Substitution of natural coral by cortical bone and bone marrow in the rat femur (Part I).
Journal of Materials Science Materials in Medicine 5, 688-691, 1994

DAMIEN C.J.,CHRISTEL P., BENEDICT J., PATAT J.L., GUILLEMIN G.*(LRO,FRANCE / Intermedics Orthopeadics, Denver, USA)*
A composite of natural coral, collagen, Bone Protein and basic Fibroblast Growth Factor tested in a rat subcutaneous model.
Annales Chirurgiae et Gynaecologiae 1993; 82:117-128
GRYNSZPAN R.I., SCHNABL O., LACROIX E., KUHLMANN J.N., DERER P.
(CNRS, Paris, FRANCE)
Etude par spectroscopie d'annihilation des positrons de biomatériaux implantés dans les tissus osseux. Actualités en Biomatériaux, Editions Romillat, 1993, 161-169.

IRIGARAY J.L., OUDADESSE H., BLONDIAUX G., COLLANGETTES D.
(CNRS de Clermont-Ferrand et Université Blaise Pascal, Aubière, FRANCE)
Kinetics of the diffusion of some elements evaluated by neutron activation in a coral implanted in vivo.
Journal of radioanalytical and nuclear chemistry, vol.169, n°2, 1993, p. 339-346.

GUILLEMIN G., PATAT J-L. *(LRO, Faculté de médecine Lariboisière, Paris, FRANCE)*
The use of coral as a bone graft substitute
J. Biomedical Materials research 1987; 21: 557-567

IRIGARAY J.L., OUDADESSE H., ELFADL H., SAUVAGE T.
(CNRS de Clermont-Ferrand et Université Blaise Pascal, Aubière, FRANCE)
Etude de la variabilité des éléments traces par radioactivité nucléaire dans un corail implanté.
Actualités en Biomatériaux, Editions Romillat, 1993, 170-174.

IRIGARAY J.L., OUDADESSE H., ELFADL H., SAUVAGE T., THOMAS G., VERNAY A.M.
(CNRS de Clermont-Ferrand et Université Blaise Pascal, Aubière, FRANCE)
Effet de la température sur la structure cristalline d'un biocorail.
Journal of thermal analysis, vol.39, 1993, p. 3-14.

IRIGARAY J.L., SAUVAGE T., OUDADESSE H., EL FADL H., DESCHAMPS N., LEFAIVRE J., BARLET J.P., TERVERS S., TIXER H.
(CNRS de Clermont-Ferrand et Université Blaise Pascal, Aubière, FRANCE)
Study of the mineralization of coral implanted in vivo by radioactive tracers.
Journal of Radioanalytical and Nuclear Chemistry, Articles 1993; Vol. 174, N°1: 93-102.

BOU-ABBOUD N., SAWAF M.H., OUHAYOUN J.P. *(Université Paris VII-Garancière, FRANCE)*
Ostéoconduction - ostéoinduction : l'apport des différents matériaux de comblement.
Actualités en Biomatériaux, Editions Romillat, 1993, 207-302.

ARNAUD E., DE VERNEJOUL M.C., MOLINA F. *(Hôpital Necker, Paris, FRANCE)*
Potentialization of Bone Growth Factor (TGF-β1) with Natural Coral Skeleton and Fibrin Glue. Experimental and preliminary clinical results.
Proceedings of the fifth int. congress of the int. society of cranio facial surgery. Mexico, 1993.

OHGUSHI H., OKUMURA N., YOSHIKAWA T., INOUE K., SENPUKU N., TAMAI S. *(Nara Medical University, JAPAN)*
Bone formation process in porous calcium carbonate and hydroxyapatite
Journal of Biomedical Materials Research, 1992; 26: 885-895

OUHAYOUN J.P, ISSAHAKIAN S., PATAT J.L., SHABANA A.H.M.,
GUILLEMIN G. *(Université Paris VII-Garancière, FRANCE)*
Histological Evaluation of natural Coral Skeleton as a Grafting Material in miniature swine mandible.
Journal of Materials Science : materials in medicine, n° 3, 1992, p.222 - 228.

SAUVAGE T. *(Université de Clermond II , FRANCE)*
Etude par des méthodes nucléaires d'analyse des transformations physico-chimiques du corail implanté in vivo.
Thèse de doctorat d'université, spécialité physique nucléaire, université Clermond II (France), 1992.

RYGT A.
Recherches sur les oligo-éléments: importance du Sr,Zn.
Bulletin Soc. Chem. Biol. 31, 1974, 1052-1061.

ROSENTHAL H.L – COCHRAN O.A.
Strontium content of mammalian bone – Diet and excreta.
Environmental Research, 5 (2), 1972, 182-191.

GROSS U., VOIGT C., MULLER-MAI *(Free University of Berlin, GERMANY)*
Comparative Morphology of the Bone Inter-face with Glass Ceramics, Hydroxyapatite and natural Coral
The Bone Biomaterial Interface, Ed. J.E. Davis, University of Toronto press, 1991; 308-320.

LOGEART – AVRAMOGLOU D., ANAGNOSTOU F., BIZIOS R., PETITE H.
(LRO, faculté de médecine Lariboisière saint- Louis, université Denis Diderot)
Engineering bone: challenges and obstacles
J. Cell Mol. Med. Vol. 9, No 1, 2005 pp. 72-84

PETITE H.P., SEDEL L, OUDINA K., BOUSSON V., VIATEAU V., HANNOUCHE D., LOGEART – AVRAMOGLOU D.,
(Ecole national vétérinaire d'Alfort, Laboratoire de recherches orthopédiques, Université D.Diderot, laboratoire de radiologie expérimentale)
Long- bone critical- size defects treated with Tissue- engineered Grafts: A study on sheep
Journal of Orthopedic Research society 2007, published by Willy InterScience,

PETITE H.P., BLANCHAT C., OUDINA K, SEDEL L, BENSAID W, D.V.S.,M.S.,VIATEAU V., Ph.D. , POTIER E., BOUSSON V., M.D., B.S., GUILLEMIN G.
De Novo Reconstruction of functional bone by tissue engineering in the metatarsal sheep model
The journal of Tissue Engineering .vol. 11, Number 5/6, 2005

PETITE H.P., BLANCHAT C., TRIFFITT J.T, OUDINA K, SEDEL L, BENSAID W. *(UMR. -CNRS, Faculté de médecine Lariboisière saint – Louis, université D.Diderot)*. Biomaterials 11 December 2002
A biodegradable fibrin scaffold for mesenchymal stem cell transplantation

IX.2. CLINICAL RESEARCH - ORTHOPAEDICS AND SPINE SURGERY

E. SOFFER[1]., J.P. OUHAYOUN.[2], A. MEUNIER[1], F. ANAGNOSTOU[2]
Effects of Autologous Platelet Lysates on Ceramic Particle Resorption and New Bone Formation in Critical Size Defects: The Role of Anatomical Sites
[1] Laboratoire Biomatériaux et Biomécanique Ostéo-articulaires, UMR.-A-C.N.R.S. 7052, Paris, France
[2] Département de Parodontologie, Faculté de Chirurgie Dentaire Université Paris 7 et Laboratoire Biomatériaux et Biomécanique Ostéo-articulaire, U.M.R.-C.N.R.S. 7052, Paris, France
Received 25 March 2005: revised 8 September 2005: accepted 26 October 2005.
Published online 16 March 2006 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jbm.30516

W. BENSAID[a,b], J.T. TRIFFITT[b], C. BLANCHAT[a], K. OUDINA[a], L. SEDEL[a], H. PETITE[a,*]
A biodegradable fibrin scaffold for mesenchymal stem cell transplantation
[a] Laboratoire de Recherches Orthop!ediques, UMR-CNRS 7052, Facult!e de M!edecine Lariboisi"ere Saint-Louis, Universit!e D. Diderot, 10 avenue de Verdun, Paris 75010, France
[b] Botnar Research Laboratory, Nuffield Department of Orthopaedic Surgery, University of Oxford, UK
Received 5 September 2002; accepted 11 December 2002

W. BENSAÏD, D.V.S.,1 K. OUDINA, M.S.,1 V. VIATEAU, D.V.S., Ph.D.,1,2 E. POTIER, M.S.,1
V. BOUSSON, M.D.,1 C. BLANCHAT, B.S.,1 L. SEDEL, M.D.,1
G. GUILLEMIN, Ph.D.,1 and H. PETITE, Ph.D.1
De Novo Reconstruction of Functional Bone by Tissue Engineering in the Metatarsal Sheep Model
TISSUE ENGINEERING, Volume 11, Number 5/6, 2005

D. LOGEART-AVRAMOGLOU, F. ANAGNOSTOU, R. BIZIOQ, H. PETITE*
Engineering bone: challenges and obstacles
Laboratoire de Recherches Orthopédiques, Faculté de Médecine Lariboisière Saint-Louis, Université Denis Diderot, Paris, France
Received: December 22, 2004; Accepted: January 25, 2005
J. Cell. Mol. Med. Vol 9, No 1, 2005 pp. 72-84

Veronique VIATEAU,1 Genevieve Guillemin,2 Valerie BOUSSON,3 Karim OUDINA,2 Didier HANNOUCHE,2 Laurent SEDEL,2 Delphine LOGEART-AVRAMOGLOU,2 Herve PETITE2
1 Ecole Nationale Ve´te´rinaire d'Alfort, 7 avenue de Gaulle, 94700 Maisons Alfort, France
2 Laboratoire de Recherches Orthopédiques, Centre Nationale de la Recherche Scientifique-Sciences pour l'Ingénieur, Unité Mixte de Recherche 7052, Faculté de Médecine Lariboisiére Saint-Louis, Université Denis Diderot, 10 avenue de Verdun, 75010 Paris, France
3 Laboratoire de Radiologie Expérimentale, Centre Nationale de la Recherche Scientifique-Sciences pour l'Ingénieur, Unité Mixte de Recherche 7052, Faculté de Médecine Lariboisiére Saint-Louis, Université Denis Diderot, Paris, France
Received 12 May 2006; accepted 30 October 2006
Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jor.20352

Herve PETITE*, Veronique VIATEAU, Wassila BENSAÏD, Alain MEUNIER, Cindy dE POLLAK, Marianne BOURGUIGNON, Karim OUDINA, Laurent SEDEL and Genevieve GUILLEMIN
Tissue-engineered bone regeneration
Laboratoire de Recherches Orthopédiques, CNRS UPRES A 7052, Université D. Diderot, Faculté de Médecine Lariboisière Saint-Louis, 10 avenue de Verdun, 75010 Paris, France. *Corresponding author (hpetite@infobiogen.fr).
Received 17 February 2000; accepted 19 May 2000

E. ARNAUD[a], C. DE POLLAK[b], A. MEUNIER[b], L. SEDEL[b], C. Damien[c], H. PETITE[b,*]
Osteogenesis with coral is increased by BMP and BMC in a rat cranioplasty
[a] Unite& de chirurgie craniofaciale, De& partement de neurochirurgie, HoLpital Necker, 75743 Paris cedex 15, France
[b] Laboratoire de Recherches Orthope& diques, Universite& D. Diderot, Paris VII, URA CNRS 1432, 10 ave. de Verdun 75010 Paris, France
[c] Sulzer Orthopedics, 4056 Youngxeld Street, Wheat Ridge, CO 80033, USA
Received 30 November 1998; accepted 16 May 1999

CIROTTEAU Y. *(Clinique de l'Alma, Paris, FRANCE)*
A physiological approach in stabilization and consolidation of unstable femoral neck fracture in osteoporotic elderly patients: a retrospective review
Eur J Orthop Surg Traumatol; 2003; 13:145-155

CIROTTEAU Y. *(Clinique de l'Alma, Paris, FRANCE)*
Behavior of natural coral in a human osteoporotic bone
Eur J Orthop Surg Traumatol; 2001; 11:149-160

K. GHIAMPHY K., F. GOSSET and P. KHER *(Université Louis Pasteur, Strasbourg, FRANCE)*
Coral grafts used in cervical interbody fusions
Eur J Orthop Surg Traumatol; 1999; 9:209-222

CIROTTEAU Y. *(Hôpital de Courbevoie-Neuilly-sur-Seine, FRANCE)*
Upper femoral metaphysis morphological modifications of a human struck down by osteoporotic disease.
C.R. Acad. Sci. Paris, Sciences de la vie / Life Sciences; 1999; 322:401-411

KEHR P, GRAFTIAUX A.G., GOSSET F. *(Université Louis Pasteur, Strasbourg, FRANCE)*
The use of coral for cervical interbody arthrodesis (IBA) and vertebral body excision.
Orthopedie, Traumatologie, Vol 7, n° 2, 1997.

KEHR P., GRAFTIAUX A., BENCHEIKH K. *(Hôpital Universitaire de Strasbourg, FRANCE)*
Use of coral in cervical intersomatic grafting
Bulletin de l'Institut Océnographique, Numéro spécial 14,3 - 1995.

CIROTTEAU Y. *(Hôpital de Courbevoie-Neuilly-sur-Seine, FRANCE)*
The use of biocoral for hip fracture repair in elderly patients
Bulletin de l'Institut Océnographique, Numéro spécial 14,3 - 1995.

CIROTTEAU Y. *(Hôpital de Courbevoie-Neuilly-sur-Seine, FRANCE)*
Modifications morphologiques de la diaphyse d'un os long chez l'adulte.
Déductions thérapeutiques théoriques.
La Lettre Chirurgicale, supplément Orthopédie-Traumatologie - 1994, n° 128.

PENAUD J., MARTIN G., MILLER N., MOLE C., BABEL L., AUBRY B.
(Faculté de Chirurgie Dentaire de Nancy, FRANCE)
Implantation immédiate : membrane de collagène et/ou biomatériaux.
Actualités en Biomatériaux, Editions Romillat, 1993, 251-254.

PATAT J.L., GUILLEMIN G.
(LRO, Faculté de médecine Lariboisière, Paris, FRANCE)
Le corail naturel utilisé comme substitut de greffon osseux. Applications cliniques en chirurgie orthopédique et traumatologique.
Actualités en Physiopathologie et Pharmacologie Articulaires, Masson, 1993, 514-519.

KEHR P., GRAFTIAUX A., GOSSET F. *(Hôpital Universitaire de Strasbourg, FRANCE)*
Coral as graft in cervical spine surgery.
European Journal of Orthopaedic Surgery & Traumatology, 1993 3:287-293.

CIROTTEAU Y. *(Hôpital de Courbevoie-Neuilly-sur-Seine, FRANCE)*
Reconstruction des pertes de substances osseuse cotyloidiennes et fémorales lors de reprises de PTH à l'aide de corail naturel.
Actualités en Biomatériaux, Editions Romillat, 1993, 179-187.

KHAVARI F., BAJPAI P.K. *(University of Dayton, USA).* Biomedical Science Instrumentation, vol.29, 1993.
Coralline-sulfate bone substitutes.

ZAIOUR W., DEHOUX E., DEPREY F., SEGAL Ph.
(Centre Hospitalier Universitaire de Reims, FRANCE)
Use of coral as a bone graft substitute for anterior fusion of the lower cervical spine. A review of twenty cases.
Orthopaedic Product News, May/June 92

PATAT J.L., POULIQUEN J.C., GUILLEMIN G.
(LRO, Faculté de médecine Lariboisière, Paris, FRANCE)
Le corail naturel utilisé comme substitut de greffon osseux, son rôle dans les économies de sang dans la chirurgie du rachis.
Acta orthopaedica Belgica, Vol 58 - Suppl I - 1992.

PATAT J.L., POULIQUEN J.C., GUILLEMIN G.
(LRO, Faculté de médecine Lariboisière, Paris, FRANCE)
Biocoral, a biomaterial for bone grafts applications in surgery of the spine
Orthopaedic Product News, Medical Magazine, UK, January 1992.
KEHR P., GRAFTIAUX A. *(Hôpital Universitaire de Strasbourg, FRANCE)*
Résultats à long terme des ostéophytectomies cervicales transdiscales
Orthop Traumatol, 1991,1: 81-86.

POULIQUEN J.C., JEAN N., NOAT M,*(Hôpital Raymond Poincaré, Garches, FRANCE)*
Les economies de sang en orthopédie pédiatrique
Chirurgie, 1990, 116: 360-369

POULIQUEN J.C., NOAT M, VERNERET C. *(Hôpital Raymond Poincaré, Garches, FRANCE)*
Le corail substitué à l'apport osseux dans l'arthrodèse vertébrale postérieure chez l'enfant
Revue de Chirurgie Orthopédique 1989; 75: 360-369

POULIQUEN J.C., NOAT M, VERNERET C. *(Hôpital Raymond Poincaré, Garches, FRANCE)*
Coral as a substitute for bone graft in posterior spine fusion in childhood
The French journal of orthopaedic Surgery, 1989, 3, n°3: 360-369

IX.3. CLINICAL RESEARCH - MAXILLOFACIAL SURGERY

ARNAUD E. *(Hôpital Necker, Paris, FRANCE)*
Substitut osseux avec facteur de croissance. Cas cliniques préliminaires pour les indications cranio- et maxilo-faciales.
Ann Chir *Plast Esthét 1998;43;n°1:40-50*

BOUTAULT F. *(Centre Hospitalier Universitaire de Toulouse, FRANCE)*
Intérêt des blocs de corail dans les plasties d'augmentation des pommettes. Etude prospective portant sur 23 patients.
Annales de chirurgie plastique, 1997, 42 (3), 216-222

MERCIER J., PIOT B., GUEGEN P. *(Université de Nantes, FRANCE)*
Le plancher orbitaire en corail. Son intérêt en traumatologie.
Rev. Stomatol. Chir. maxillofac, 1996, n° 6, pp 324-331

SOOST F. *(University of Berlin (Humbolt), GERMANY)*
Biocoral - ein alternativer knochenersatz.
Chirurg 1996; 67: 1193 - 1196

SOOST F. *(University of Berlin (Humbolt), GERMANY)*
Historischer Überblick der Knochenersatz-und Implantat-materialien in der craniofacialen Chirurgie
OSTEOLOGIE 1996; 135 - 143

SANDOR G., MARCHAC D. *(Hospital of sick children, Toronto, CANADA)*
Experience with the use of coral granules as a bone graft substitute in the human cranio-maxillofacial skeleton.
Bulletin de l'Institut Océanographique, Monaco, 1995; 14, 3.

CHEVALIER D., LANCIAUX V. *(Hôpital Claude-Huriez, Lille, FRANCE)*
Intérêt de l'implant de corail dans le traitement des échecs fonctionnels après laryngectomie subtotale avec crico-hyoido-pexie.
Ann. Oto-Laryngol. Chir. Cervicofac. (Paris), 1994; 111: 208-210.

MARCHAC D., SANDOR G. *(Hospital Necker, Paris, FRANCE)*
Use of coral granules in the craniofacial skeleton.
The Journal of Craniofacial Surgery, Vol. 5, Number 4, September 1994.

LOTY B., ROUX F.X., GEORGE B. *(Centre Hospitalier Universitaire Cochin, Paris, FRANCE)*
Utilisation du corail en chirurgie osseuse
.International Orthopaedics 1990; 14: 255-259.

LEVET Y., GUERO S., JOST G. *(Hôpital Lariboisière, Paris, FRANCE)*
Utilisation du corail en remplacement des greffes osseuses en chirurgie faciale, Quatre ans de recul
Ann. Chir. Plast. Esthét. 1988; 33, n°3:279-282

SERVERA C., SOUYRIS F., PAYROT C., JAMET P.
(University Hospital Centre Montpellier, FRANCE)
Le corail dans les lésions infra-osseuses, Bilan après 7 ans d'utilisation
Rev. Stomatol.Chir. maxillofac. 1987; 5: 326-333

SOUYRIS F., PELLEQUER C., PAYROT C., SERVERA C.
(University Hospital Centre Montpellier, FRANCE)
Coral, a New Biomedical Material, Experimental and First Clinical Investigations on MadreporariaJ.
max.fac. Surg. 1985; 13: 64-69

VOREAUX P., JOST G., LEVET Y., RICHARD P.
(Université Paris VII et Hôpital Lariboisière, Paris, FRANCE)
Utilisation de squelettes de coraux en chirurgie réparatrice de la face et des maxillaires
Le chirurgien dentiste de France 1984; n°265: 59-63
LEVET Y., JOST G. (*Hôpital Lariboisière, Paris, FRANCE)*
Utilisation de squelette de coraux madréporaires en chirurgie réparatrice
Ann. Chir. Plast. Esthét. 1983; 28, n°2:180-181

PETITE H.P., SEDEL L, MEUNIER A., DAMIEN C., DE POLLAK, ARNAUD E.
(LRO, Université D.Diderot), Biomaterials 16 May 1999
Osteogenesis with coral is increased by BMP and BMC in a rat cranioplasty

IX.4. CLINICAL RESEARCH - ENT SURGERY

CHEVALIER D., LANCIAUX V., DARRAS J-A., PIQUET J-J.
(Hôpital Claude-Huriez, Lille, FRANCE)
Intérêt de l'implant de corail dans le traitement des échecs fonctionnels après laryngectomie subtotale avec crico-hyoido-pexie.
Ann. Oto-Laryngol. Chir. Cervicofac.(Paris), 1994, 111: 208-210

SCHMOLL L., DEBRY Ch., BOULLION F. (Hôpital Civil, Strasbourg, FRANCE)
Utilisation de matériaux madréporaires en chirurgie otologique. Etude préliminaire.
Ann. Oto-Laryng. (Paris), 1990, 107: 67-70

ROBIER A., GEOFFROY Ph. de, PANDRAUD L., GOGA D., BEUTTER R.
(Hôpital Trousseau, Tours, FRANCE)
Utilisation des implants coralliens en chirurgie oto-rhino-laryngologique et maxillo-faciale.
Ann. Oto-Laryng. (Paris), 1987, 104: 303-306

GEOFFROY Ph. De, (Université François Rabelais, Tours, FRANCE)
Bilan de l'utilisation d'implants de corail madréporaire en chirurgie oto-rhino-laryngologique et maxillo-faciale.
Thèse de doctorat de médecine, Tours, 1986, n° 165

IX.5. CLINICAL RESEARCH - ORAL SURGERY

YUKNA R. A. *(Louisiana State University, USA)*
A 5 year follow-up of 16 patients treated with coralline calcium carbonate (BiocoralTM) bone replacement grafts in infrabony defects.
J. Clin Periodontol 1998; 25: 1036-1040

CORRENTE G. (University of Turin, ITALIA)
Supracrestal Bone Regeneration around dental implants using a Calcium Carbonate and a Fibrin-Fibronectin sealing system : Clinical and Histologic evidence.
Int. J. Periodontics & Restorative Dentistry, 1997; 17, 171-181.

OUHAYOUN J.P,(Université Paris VII-Garancière, FRANCE)
Bone grafts and Biomaterials used as bone graft substitutes
II European Workshop in Periodontics, Switzerland, Quintessenz Verlag, 1996; 313-348

OUHAYOUN J.P,(Université Paris VII-Garancière, FRANCE)
Apport des implants dans la thérapeutique parodontale.
J. Information dentaire 1996; 10: 699-704

COCHET J.Y, GIROMANY. (Paris, FRANCE)
Chirurgie endodontique : utilisation des matériaux de comblement et des membranes.
Première partie : greffes et matériaux de substitution osseuse.
Revue d'Endodontie, Vol 14 n° 1, Avril 1995

COCHET J.Y. (Paris, FRANCE)
Matériau de comblement en endodontie
Tribune dentaire, Vol 3 n° 4, 1995

COCHET J.Y. (Paris, FRANCE)
Lésions endo-parodontales
Tribune dentaire, Vol 3 n° 11, 1995

ISSAHAKIAN S. (Paris, FRANCE)
Espacement d'un biomatériau.
Tribune dentaire Vol 2, n° 3, Février 1995.

MORA F, OUHAYOUN J.P (Université Paris VII-Garancière, FRANCE)
Clinical evaluation of natural coral and porous hydroxyapatite implants in periodontal bone lesions :
Results of 1 year follow-up.
J. Clinical Periodontol 1995 : 22: 877-884

YUKNA R. A. (Louisiana State University, USA)
Clinical evaluation of coralline calcium carbonate (BIOCORAL) as a bone replacement graft material in human periodontal osseous defects.
Journal Periodontol, February 1994, Vol 65 - Nb. 2, pp 177-185.

BELLIEN P. (FRANCE)
Cas complexe d'une incisive maxillaire
Tribune dentaire 1994, Vol 2, n° 20, 14-21

HIPPOLYTE M.P., FABRE D. (Faculté de Montpellier, Avignon, FRANCE)
Membrane non résorbable et corail.
Tribune dentaire, Vol 2, n°3, Février 1994

LUCAS A., MICHEL J.F. (Faculté des Sciences de Rennes, FRANCE)
Le corail madréporaire utilisé en chirurgie parodontale. Etude ultrastructurale.
Tribune dentaire, Vol 2, n° 3, Mai 1994

BUCCI SABATTINI V., LUCCONI G., GIORDANO A. (University of Varese, ITALIA)
Biomateriale in chirurgia parodontale: il biocoral® nella rigenerazione guidata del parodonto profondo.
J. Nuova Proposta 1991-01

BUCCI SABATTINI V., BARTOLLUCCI E.G. (University of Varese, ITALIA)
Il rialzo del pavimento del seno mascellare ad uso implantare: tecnica chirurgica
J. Nuova Proposta 1991-2

ZERBIB R., OUHAYOUN J.P., FREYSS G. (Université Paris VII-Garancière, FRANCE)
Apport Osseux et chirurgie implantaire
J. Parodontologie 1991; 10:177-188

LOUISE F., BORGHETTI A. (Faculté de Marseille, FRANCE)
Evaluation clinique de l'implantation d'un corail naturel dans des défauts osseux parodontaux, Résultats à un an
J. Parodontologie 1991; 10:69-76

OUHAYOUN J.P., ETIENNE D. (Université Paris VII-Garancière, FRANCE)
Comblement immédiat des sites d'extraction en omnipratique: utilisation d'un biomatériau résorbable, le corail naturel.
J. L'Information Dentaire 1989; 4: 225-238

NEAU A
Restauration prothétique des incisives maxillaries extraites à lasuite d'une parodontite
Stratégie prothétique, avril 2004, vol 4, n°2, p. 129-139