The Concept of Induced Membrane for Reconstruction of Long Bone Defects

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The Concept of Induced Membrane for Reconstruction of Long Bone Defects

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KEYWORDS

• Bone reconstruction • Bone defect • Membrane
• Osteoinductive factors • Bone healing

The reconstruction of wide long bone diaphyseal defects is often the major challenge in limb salvage whatever the etiology of bone loss. The most common and widely accepted procedures are the vascularized bone free transfer and the Ilizarov bone transport method. Bone autograft is not advocated when the defect is over 4 to 5 cm. When diaphyseal defects larger than 6 cm are reconstructed with autologous bone graft, healing is incomplete because of graft resorption even in a good vascularized muscular envelope.[1,2] Experimental study and clinical experience concerning osteoperiosteal flaps were encouraging,[3] but the limited sizes of harvested flaps on the human body incited the authors to abandon this technique of bone reconstruction

Since 1986, the authors' routinely use a technique that has permitted the authors to elaborate the concept of induced membrane and to reconstruct large defects with nonvascularized bone autograft.[4,5] Induced membrane is different from the bioresorbable polylactide membranes experimentally tested to treat critical size, segmental defects in rabbits[6] or sheep.[7,8]

The aim of this article is to present the membrane as a biological model, to compare the results of two clinical series, and to discuss the implications of the model.

PRINCIPLES OF TECHNIQUE

The reconstruction needs to have two different operative stages (**Fig. 1**). The first stage is comprised of a radical debridement, a soft-tissue repair by flaps when needed, and the insertion of a polymethyl methacrylate (PMMA) cement spacer into the bone defect. The second stage is performed 6 to 8 weeks later, when the definitive healing of soft tissue is acquired. The spacer is removed, but the membrane that is induced by the cement is left in place **Fig. 1**A. The cavity is filled up by morcellized cancellous bone autograft harvested from the iliac crests **Fig. 1**B. Sometimes, when the amount of autograft is not sufficient or to spare an iliac crest, bone substitute (demineralized ox bone) is added to the cancellous bone according to a ratio that is not over 1:3.

Several technical details should be emphasized. At the first stage, the cement must be wrapped around the bone extremities to allow detaching small pieces of the ends of the bone and lifting it with a bit of the induced membrane, at the second stage. When the bone graft is placed into the tube, the soft tissues, including the membrane, are sutured close to the graft resulting in a containment system **Fig. 1**C. When treating a diaphyseal defect of the tibia, the cement is applied on the fibula as far as possible to obtain a very strong reconstruction. Moreover, at the second stage, the authors routinely perform an intertibiofibular graft at both extremities of the tibial defect, by a posterior approach **Fig. 1**D. In reconstruction of the lower limb, the full weight bearing is usually authorized to patients at 5 to 6 months with the protection of the external fixator. Then the fixation is dynamized during 1 month and

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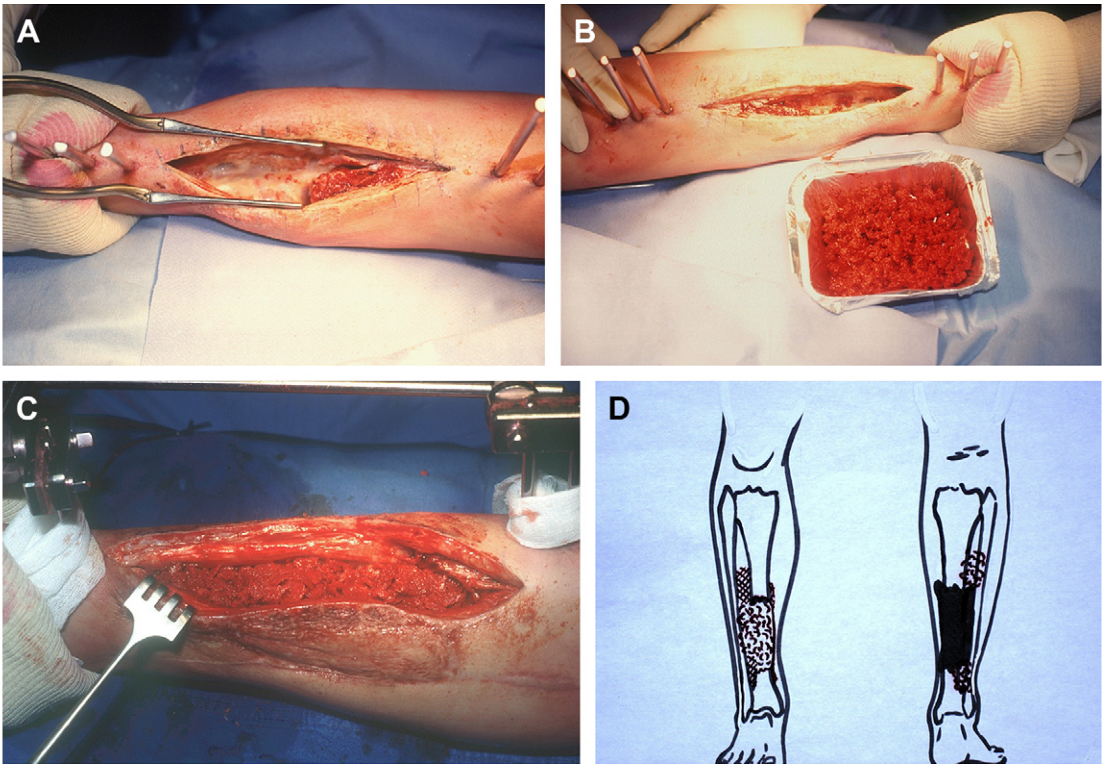

Fig. 1. Elements of technique. (*A*). The preoperative aspect of the membrane just before filling up the cavity Note the petaling of the bone extremity. (*B*) Morcellized cancellous bone graft; the chips should be as small as possible. The alveolar structure of the cancellous bone permits a fast revascularization by the vascular buds issued from the membrane. (*C*) The cavity is filled up; the suture en bloc of the membrane and subcutaneous tissue results in a containment system. (*D*) Principles of reconstruction of the tibia. At the first stage the PMMA spacer is applied on the fibula. At the time of reconstruction an intertibiofibular graft is performed on both extremities.

finally removed 1 month later. In 1990, the surprising results of the authors' first cases incited them to undertake experimental and fundamental studies to elucidate the role of the membrane induced by the cement spacer. One of the main interrogations concerned the absence of resorption of the autograft.

The Foreign Body-induced Membrane

Initially, the role of the cement spacer was to avoid the collapse of the soft tissue into the bone defect and to prepare the bone reconstruction. Moreover, as most of the authors' clinical cases were post-traumatic septic nonunions, the spacer was considered an excellent witness of successful debridement in the absence of recurrent infection after 2 months. The initial reason for which the authors' did not excise the membrane was to prevent excessive bleeding. Finally, the main role of the cement is biological, by inducing a foreign-body surrounding membrane.

The first step of the investigation was to confirm the role of the membrane. Experimental study was done at the AO Development Institute of Davos[9] and it was asserted that the membrane avoided the resorption of the cancellous bone and had a positive effect upon the healing of the autograft. Material comprised 30 sheep on which a segmental femoral defect, 3 cm in length, was created, filled up with a PMMA cement spacer, and stabilized with a plate. One month later, four groups were constituted after removing the spacer:

- Group A: the membrane was maintained and filled up with cancellous bone chips.
- Group B: the membrane was excised and the defect was filled up with cancellous bone chips.
- Group C: the membrane alone was maintained without filling.
- Group D: the membrane was excised and the defect was not filled up.

As expected, no bone formation was noted in groups C and D. In group B, bone healing was partially obtained with an important resorption in all cases. In group A, bone healing was acquired without reduction of the volume of the initial graft.

The second step of the investigation was to precise the role of the membrane by evaluating its histologic and biochemical characteristics.[10] Histologic and immunochemistry studies were performed and the following data have been established:

- The membrane is richly vascularized in all its layers.
- The inner part (face to the cement) is a synovial like epithelium and the outer part is made of fibroblasts, myofibroblasts, and collagen.
- The membrane secretes growth factors: high concentration of VEGF and TGF Beta 1 were observed as early as the second week. BMP-2 is at its highest level at the fourth week.

Finally, membrane extracts stimulated bone marrow cell proliferation and differentiation to osteoblastic lineage.

Clinical experience showed that the cancellous bone inside the membrane is not submitted to resorption. As shown by a case report,[11] after healing, macroscopic examination of transverse

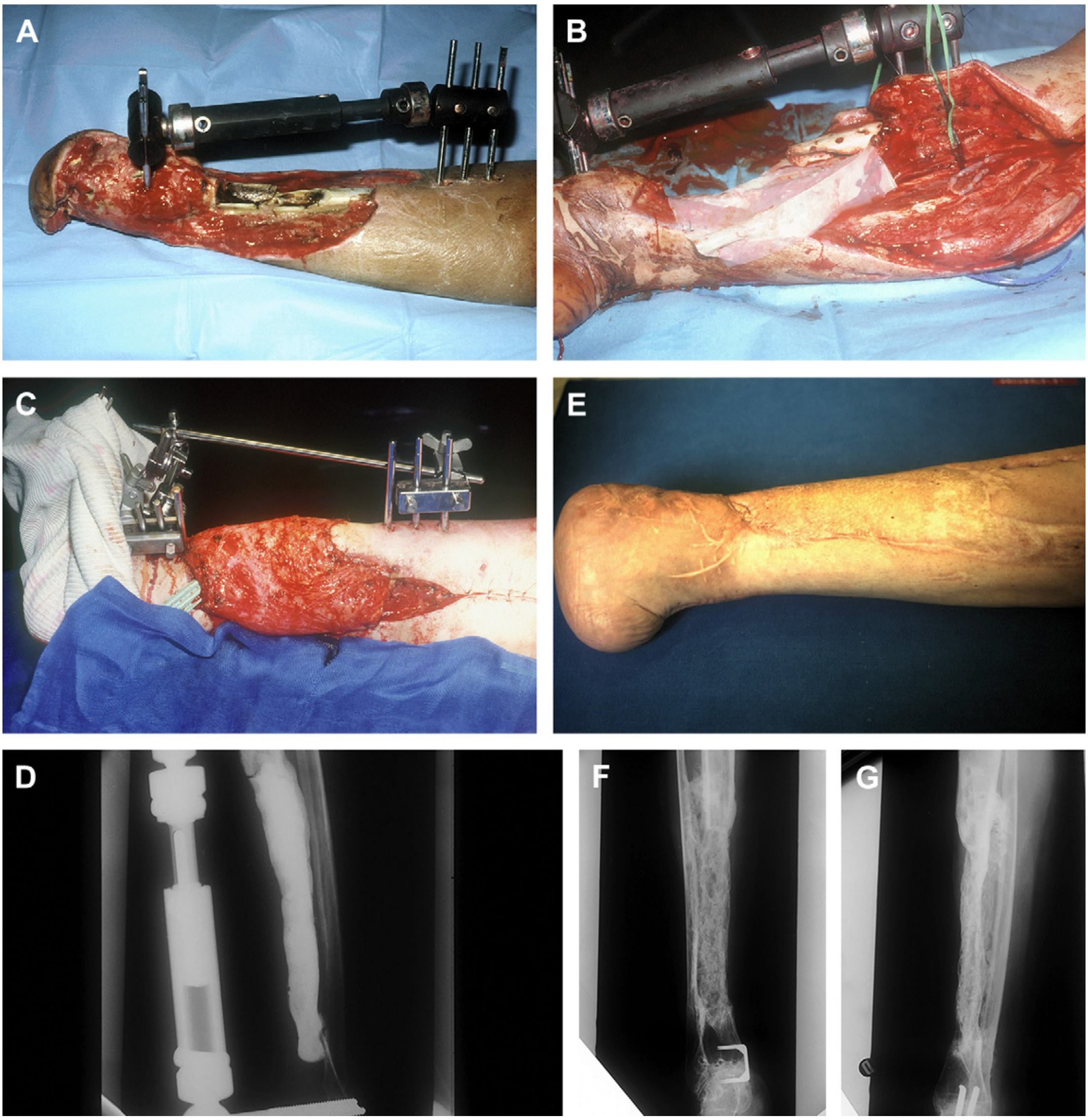

Fig. 2. Infected nonunion of the leg in a 27-year-old woman. The fore foot was amputated but the stump was sensible. (*A*) Initial aspect. (*B*) Radical debridement and preparation of the proximal vessels for covering with a free flap. (*C*) Latissimus dorsi in place. (*D*) The cement spacer under the muscle flap. Defect was 18 cm length. (*E*) Final clinical result. (*F, G*) Radiologic aspect 1 year later. Full weight bearing was permitted at the end of 6th month.

section of the healed bone graft exhibits normal bone anatomy, and the junction between the normal bone and the graft was difficult to see by macroscopic examination of longitudinal sections.

RETROSPECTIVE CLINICAL EXPERIENCE

Between 1986 and 1999,[4] the authors did a series of 35 reconstructions of long bone segmental defects ranging from 5 to 24 cm after debridement. Lower limb was involved in 29 cases and the majority of cases were posttraumatic septic nonunions of the leg (23 cases) (**Figs. 2** and **3**). Upper limb was concerned in six cases (**Fig. 4**). Soft-tissue repair by flaps was needed in 28 cases (14 free flaps and 14 pedicled flaps). Immediate complications concerned the failure of the free flaps in three patients who were treated successfully by other techniques of reconstruction (Papineau and Ilizarov procedures). In the induced membrane and grafting procedure, bone healing was regularly obtained in a time that was independent of the length of reconstruction. In all cases the authors noted an aspect of radiological healing at 4 months. At the beginning of the authors' experience, they performed additional grafts to reinforce the extremities of the reconstructed segment; but later the systematic petaling of the extremities permitted a primitive healing. At the lower limb, full weight bearing without protection was acquired in the mean time of 8.5 months (range: 6–17 months). Infection healed in all patients involved and that was probably in relation with the very radical initial debridement. In the series, the authors noted four stress fractures (2 early and 2 late) that healed by simple immobilization.

PROSPECTIVE CLINICAL STUDY

At the beginning of 2000, the authors thought that it could be interesting to associate local injection of recombinant human BMP-7 (Osigraft, Strycker, Biotech) with the bone autograft to enhance a quick formation of cortical bone.

From 2000 to 2004, 11 subjects had the two stages procedure for reconstruction of a wide diaphyseal defect. At the second stage, the morcellized cancellous bone autograft was mixed with a dose of 3.5 mg of eptotermin alpha and

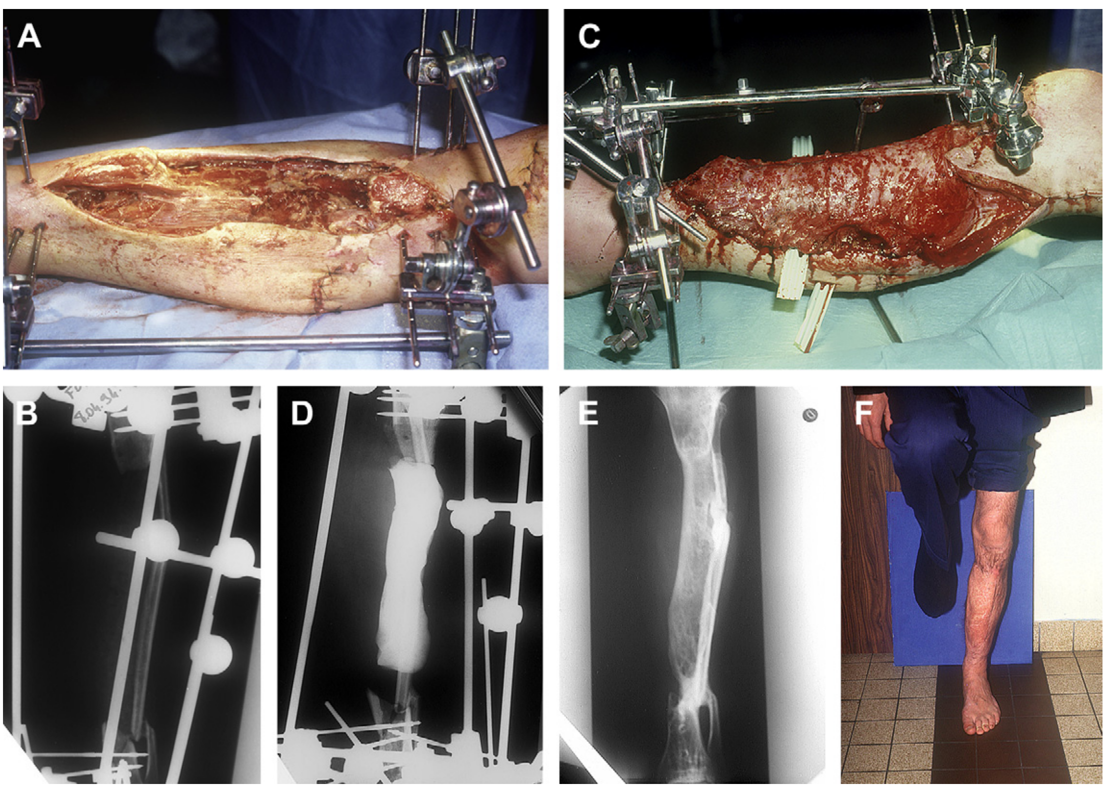

Fig. 3. Posttraumatic compound defect of the leg in a professional licensed pilot. (*A*) Initial aspect. (*B*) The segmental defect was 22 cm in length. (*C*) Soft-tissue envelope repair by a free flap. (*D*) The cement spacer under the flap. (*E*) Aspect of the reconstruction 2 years later; note the densification of the medial part of the graft according to Wolf's law. (*F*) Clinical aspect; this young man has succeeded in retrieving his license.

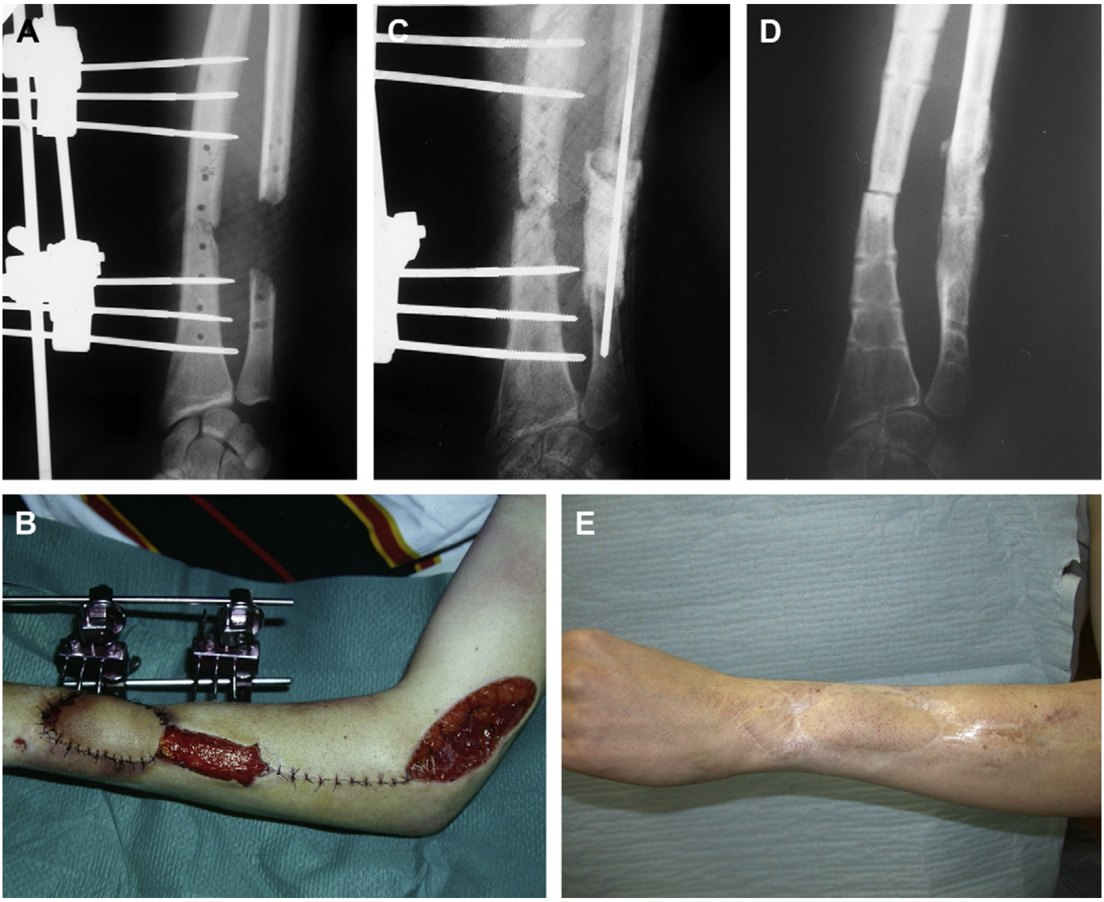

Fig. 4. Infected fracture of the forearm. (*A*) A segment of ulna was resected. (*B*) The soft- tissue defect was repaired by a custom made flap, the pedicle of which being supplied by the proximal cutaneous branch of the posterior interosseous artery. (*C*) The cement spacer under the flap. (*D*, *E*) Reconstruction healing and clinical aspect.

the preparation was left to the convenience of each surgeon. The series included 9 men and 2 women aged from 22 to 52 years (average 31). All the etiologies were posttraumatic septic nonunions. The segments involved were the tibia (9 cases), the femur (1case), and the humerus (1case). Bone defect ranged from 5 to 18 cm (average 10.5 cm). In eight cases the defect was segmental. Six subjects needed a soft-tissue repair by flaps (three latissimus dorsi free flaps; four muscle pedicled flaps). One subject had two pedicled flaps at the leg. Follow-up was more than 24 months for all subjects.

All flaps survived and no recurrence of infection occurred. Bone healing, implying a full weight bearing without protection for the lower segments, was obtained in the mean time of 11.5 months (6 to 18 months) for 10 subjects. One subject was amputated below the knee in a long-term evolution and a failure of consolidation. The most surprising was that three subjects developed a progressive deformity of the reconstructed tibial segment a few months after what was considered the consolidation. Despite additional healing procedures, including prolonged immobilization by cast or external fixator, or intertibiofibular graft, a partial recurrence of the deformity occurred in two cases (**Fig. 5**).

Another peculiar event was the evolution of the radiological aspect of the bone graft in all subjects. The authors noted a quick densification at 2 months, then areas of clearness appeared in the reconstructed bone, which evoked partial and localized zones of resorption. The authors' conclusion was that the results of this series were not improved compared with their previous experience and that association with growth factors induced unexpected effects.

DISCUSSION

The Use of Additional Growth Factors

Recombinant human BMP-7 and recombinant human BMP-2 have been proved efficacious in

Fig. 5. Septic nonunion of the leg in a 20-year-old man. (*A*) Radiologic aspect after the bone graft associated with BMP-7. (*B*) The consolidation was considered as acquired at 8 months despite the inhomogeneous aspect of the reconstructed bone. (*C*) A varus deformity appeared progressively. (*D*) Reduction and stabilization by an external device which was maintained for 3 months. (*E*) Partial recurrence of the deformity after removing the external fixator.

improving accelerating bone healing in orthotopic animal models.[12] The BMP target is the perivascular connective tissue cells in the host bone bed. Clinical studies have also shown the possibility to repair segmental defects of the tibia by cancellous bone graft augmented with human morphogenetic protein[13] and to augment new-bone development.[14–16]

BMP-7 has been shown equivalent to autogenous iliac crest bone graft in a randomized prospective study of tibial fracture nonunions.[17] The efficacy of BMP-2 for treatment of open tibial fractures has been shown in a prospective, randomized, controlled single-blind study[18] in accelerating bone healing and in reducing the need for secondary interventions. However, results of the authors' prospective study with BMP-7 are not encouraging.

Several reasons can be advanced to explain the absence of expected improvement with the addition of BMP-7; although several authors[18,19] claim that the bone morphogenetic protein implants have dose-dependent osteoinductive effect, the authors cannot infer that the delay of bone healing is caused by an insufficient dose of BMP. Other factors should be considered as the repartition of the BMP device inside the graft, the effect of postoperative aspiration drainage, and the lack of rigidity of the stabilization afforded by an external fixator. The presence of the membrane avoids the dispersion of the BMP device in the soft tissue and concentrates the substance inside the bone graft. Therefore, one can suppose some opposite action on osteoblast differentiation between TGF Beta 1 and BMP-7; although opposite effects have only been shown between TGF Beta 1 and BMP-2.[20]

On the other hand, even if BMP-7 is known to stimulate proliferation and differentiation of human bone cells in vitro, a high dose of BMP-7 inhibits the ALP (alkaline phosphatase) activity in the presence of vitamin D.[21] It can be supposed that the containment system of the membrane results in too high of a concentration of the BMP device.

Finally, according to the authors' clinical experience, they cannot determine the effect of the BMP-7 device on the healing of a bone autograft placed inside a membrane. The rather disappointing results of their clinical experience have incited them to delay the procedure using the BMP-7, while waiting to determine the conditions in using growth factors.

The Concept of Induced Membrane

The concept of induced membrane opens new perspectives. According to the results of the authors' first series and the fundamental studies, it can be asserted that induced membrane acts as a biological chamber. This assertion has recently been confirmed by independent experimental work.[22]

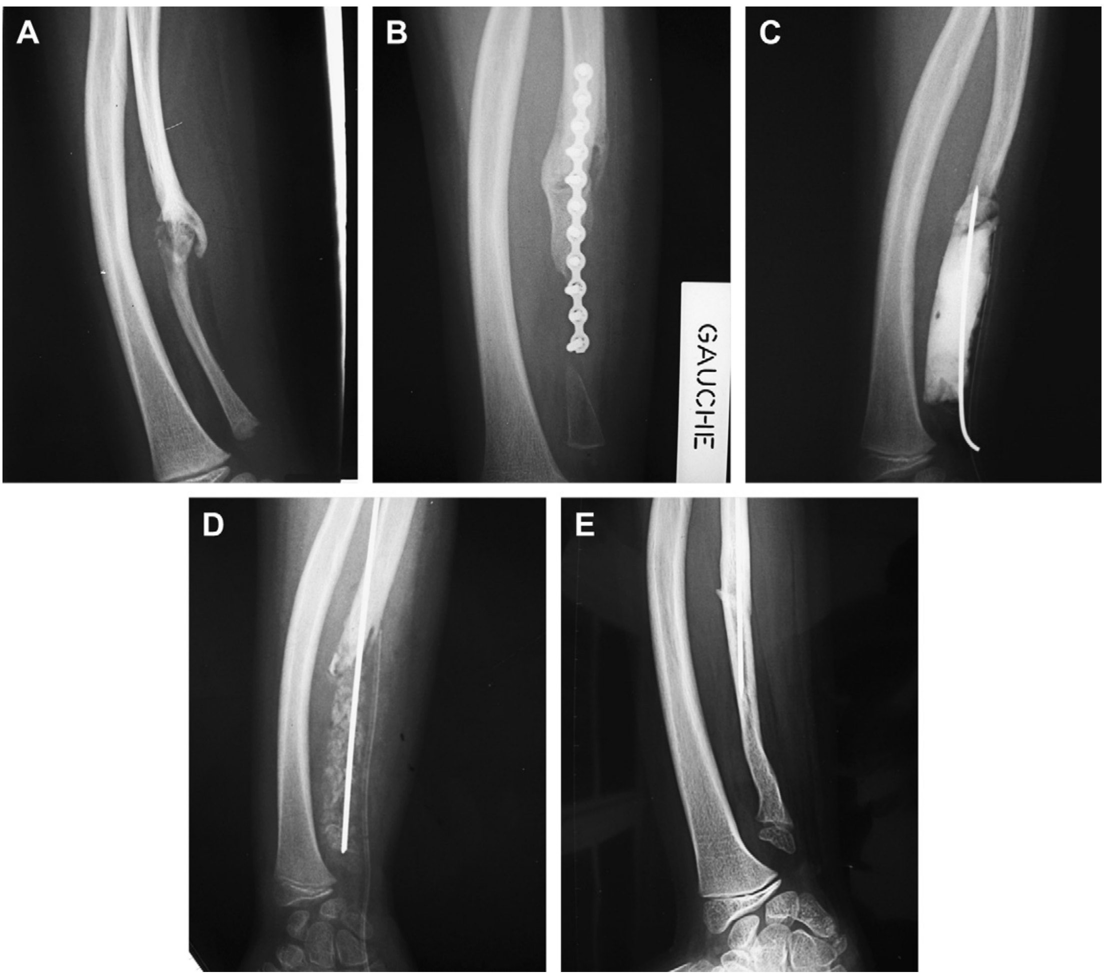

Fig. 6. Congenital pseudarthrosis of the ulna (*A*) Initial aspect. (*B*) Failure of a conventional treatment associating minimal resection, bone grafting and plating. (*C*) Radical excision sparing the distal growth plate and insertion of a cement spacer; stabilization by a wire. (*D*) Second stage; bone grafting after removing the spacer. (*E*) Radiologic aspect 3 years later; the ulnar growth plate remains open. (*Courtesy of* M.C. Romana, MD, Trousseau Hospital, Paris.)

The membrane prevents resorption of the cancellous bone while it is known that a large amount of cancellous bone placed in a richly vascularized muscular environment is partially or totally resorbed.[1,2,12] The membrane promotes the vascularization and the corticalization of the cancellous bone, even in bad vascularized bed like irradiated tissue or in very specific bone disease like congenital pseudarthrosis (**Fig. 6**). And finally, it is considered an in situ delivery system for growth and osteoinductive factors. The best period to perform the graft is 1 month after the set of the cement spacer.[9]

The induced membrane is quite different from the polylactide membranes. The latter can be used in association with a resorbable sponge[5] or cancellous bone graft.[6,7] Bone graft isolated from the soft tissue by a nonperforated membrane leads to necrosis.[7]

The conclusion of several studies is that the optimum device is a perforated, thin, and microporous membrane, and in large defects, the use of cancellous bone autograft in conjunction with fenestrated membrane produced the most consistent bone regenerate.[6,23]

However, these membranes have not been proven to secrete growth factors. Their mechanism is based on the exclusion of fibrous tissue inside the defects. Bone formation in small defects is probably supported by migration of local osteogenic cells. When cancellous bone graft is added within the lumen, small perforation of the membrane will allow the revascularization of the graft. Finally, the polylactide membranes do not have the same biological properties as the foreign body-induced membrane.

Further questions

What could be the most appropriate induced membrane according the type of the spacer? As a matter of fact, the membrane induced by a smooth implant like the PMMA cement is not exactly the same as the membrane induced by a textured implant. In the latter, synovial like metaplasia and villous hyperplasia are most developed that could enhance bone healing.

The second question is to search for other osteoinductive factors that could be secreted by the membrane. In the study of Pelissier and colleagues,[10] only the BMP-2 has been detected by a specific technique.

The third question is to determine what should be put inside the cylinder of the membrane to obtain the best reconstruction (ie, the quickest and the strongest one) from a mechanical point of view. Morcellized, fresh, cancellous bone autograft is probably the gold standard when harvested from the iliac crests. In the authors' experience[4] the bone graft harvested from the four iliac crests allows reconstruction of a diaphyseal tibial defect up to 15 to 20 cm. No morbidity was noted at the donor site because the authors harvested the cancellous bone by appropriate skin incisions without raising any cortical block. In some cases, to preserve iliac crests, the authors added bone substitute with a ratio of 1:3; the authors did not observe a difference on rate of complication or time of healing with the reconstruction performed with cancellous bone alone (**Fig. 7**). Therefore, two important questions are: (1) which ratio of bone substitute is acceptable without compromising bone healing and mechanical strength, and (2) which is the most appropriate bone substitute? In other words, is the osteoinductivity of the membrane sufficient to assume a diaphyseal reconstruction with bone substitute alone? Other possibilities are worthy of interest and should be tested in association with the procedure of the induced membrane.

- Demineralized bone matrix has important properties combining osteoconductivity and osteoinductivity.[24]
- Intramedullary canal bone reamings (ICBR) can be used as a source of viable bone graft in relation to their osteoblastic potential and living bone cells similar to bone cells from the iliac crest.[25,26] The authors have recently started a prospective series of reconstruction associating induced membrane and ICBR from the femur (**Fig. 8**).

The last question concerns the stabilization of the limb and the defect. As most of the authors' cases were septic nonunions requiring sometimes iterative excisions, they chose a preferentially external fixator, with the device being maintained until the definitive bone healing and full weight bearing, without protection, is authorized. But the external fixator does not provide an absolutely rigid fixation, which seems mandatory to favor the action of the growth factors and to obtain the fusion of the bone graft.

Moreover, when the defect exceeds 20 cm it is difficult to maintain the axis of the limb with an external device. For that reason, the authors were obliged to perform osteotomies in two patients of the first series (**Fig. 9**).[4] The best solution is probably a locked nail as it is now advocated in the treatment of recent open fractures. But the nail raised other problems as the difficulty to remove the cement and the reduction of the space devoted to the massive reconstruction.

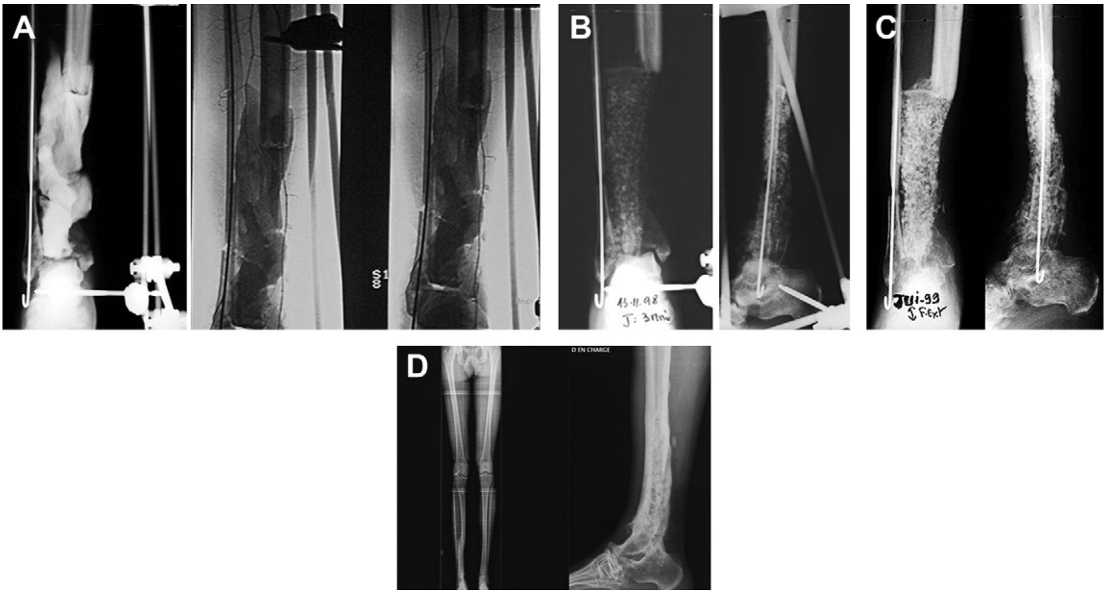

Fig. 7. Open fracture of the leg, stage IIIA Gustilo's classification. (*A*) Immediate huge bone defect—the fibula fracture was stabilized by a wire while the tibial defect was filled up with a cement spacer. (*B*) The postoperative course was uneventful, so that a huge graft was done 2 months later, consisting of fresh cancellous autograft and cancellous allograft with ratio of 50:50. Aspect of the recontruction at 3 months. (*C*) Aspect of the reconstruction at 10 months. External fixator was removed and free weight bearing was allowed. (*D*) Final result 6 years later.

SUMMARY

The authors think that the concept of membrane is well established as a bone reconstruction promotion by preventing the bone-graft resorption and by playing an important role in revascularization and consolidation. However, many problems remain to be solved relative to the stabilization, the type of material for reconstruction, the use of recombinant human growth factors, and the addition of stem cells.

Finally, this concept of membrane as a biological chamber could probably be extended to other tissular reconstruction as nerve grafting. This perspective fits in strangely with the poetic and philosophical vision of the organization of life of

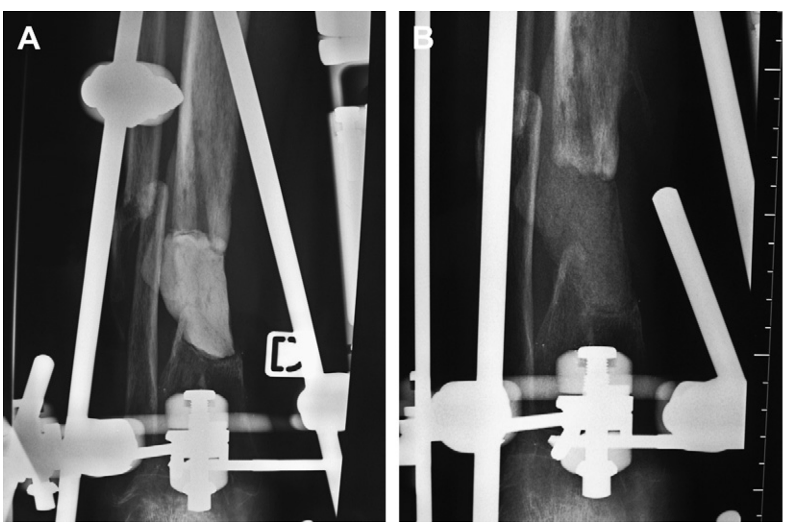

Fig. 8. Grafting from the medullar canal of the femur by the RIA procedure. (*A*) Bone defect filled up by the cement spacer. (*B*) At 3 months the graft seems well integrated. Partial weight bearing was allowed with protection of the external fixator.

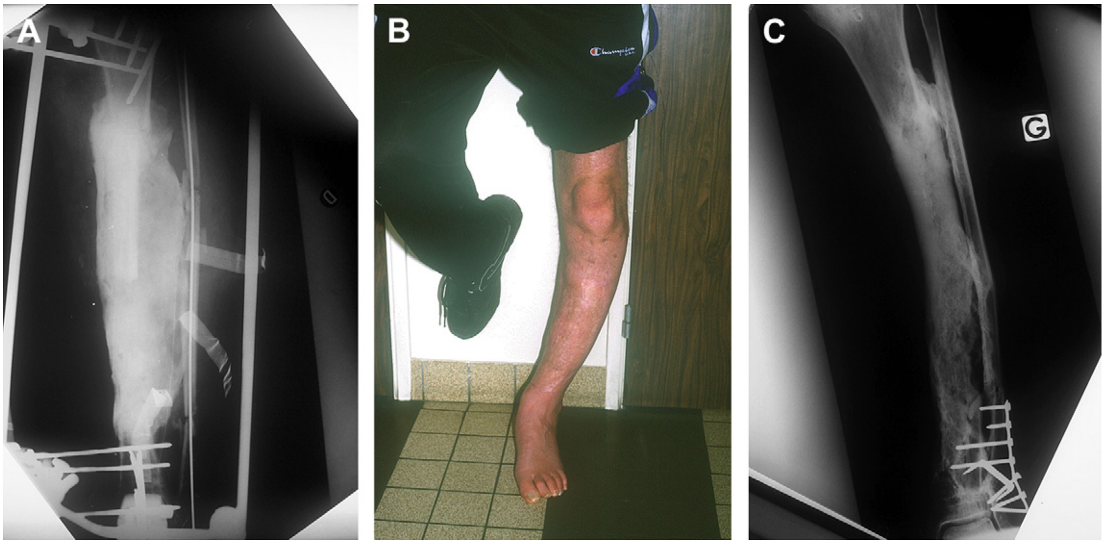

Fig. 9. Complication of a huge healed reconstruction of the tibia. (*A*) Initial bone defect was 24 cm length. (*B*) The varus deformity existed before the bone reconstruction and was caused by the difficulty to maintain the limb axis by an external fixator. Although the healing was acquired, the deformity was not acceptable from a mechanical point of view. (*C*) The correction of the deformity was obtained by a supramalleolar osteotomy.

Goethe who wrote in his book, *The Metamorphosis of Plants*: "A very important principle of the organization is that vital activity requires an envelope, which protects from the external elements. This envelope may be bark, skin, or shell, all that is living should be wrapped up."

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