2.1 Bone Healing in Rabbits

Flexible Intramedullary Nailing (FIN) is a closed internal fixation method based on the principles of primary fracture healing of nonoperative treatment. Initial fracture hematoma and periosteum, which is largely preserved, are included as part of the well-known fracture–repair process. Our experimental study in rabbits conducted in 1985 [1] confirmed that fracture healing with FIN is predominantly by periosteal callus, which forms outside of the fracture.

2.1.1 Materials and Methods

Experiments were carried out at the Laboratory of Experimental Surgery headed up by Prof. Bénichoux, University Hospital, Nancy, in 1985 and 1986. Fractures were created in rabbit tibiae under general anesthesia. Different types of mid-shaft fractures were randomly produced (i.e., simple, complex, comminuted).

These fractures were treated by closed internal fixation using two 1 mm stainless steel nails inserted through the proximal or distal metaphysis. No external immobilization was used and weight bearing was resumed immediately.

Radiographs were taken at weekly intervals for 6 weeks, then at 3 and 6 months, depending on the age of the animal at sacrifice. Histological studies were performed at d 14, 21, and 45. Bone samples were embedded without prior decalcification in methyl-metacrylate resin (Dr. Hervé Membre, Laboratory of Histology headed up by Prof. Grignon, University School of Medicine, Nancy).

All fractures united and rabbit activity did not seem to be disturbed during that period: no complications, no nonunions, no sepsis occurred.

2.1.2 Results

2.1.2.1 Radiographic Results

At week 1, no signs of ossification could be found (Fig. 2.1a), but on the 14th day, radiographs of simple fractures showed formation of dense periosteal bridging callus. Cortices were not yet healed, but bridging callus was quite strong. Radiographs of comminuted fractures began to show periosteal callus of inhomogeneous structure, and signs of intramembranous ossification (Fig. 2.2a). At week 3, the periosteal region was expanded; periosteal callus formed a sheath around bone fragments in comminuted fractures, and led to solid union in some simple fractures (Fig. 2.3). Furthermore, patency of the medullary canal was maintained due to the presence of the intramedullary nails (Figs. 2.1b and 2.2b). At 1 month, simple fractures were radiographically healed. Comminuted fractures were sheathed in a homogeneous external bridging callus, and gave an impression of stability, but the cortices were not yet fully healed (Fig. 2.2c). At week 6, good quality callus with a homogeneous structure was present, but not all cortices were fully healed (Fig. 2.1c) as evident in MRI (Fig. 2.4). At 3 months, all fracture sites were radiographically consolidated: presence of intramembranous ossification, cortical bridging, and intramedullary callus. At 6 months, the remodeling process was well under way but external
**Fig. 2.1** Comminuted fracture of the femoral shaft (rabbit) treated by flexible intramedullary nailing (FIN). Control X-rays taken at 5 days (a), 20 days (b), and 36 days (c).

**Fig. 2.2** Comminuted fracture of the femoral shaft (rabbit) treated by FIN. Control X-rays taken at 2 weeks (a), 3 weeks (b), and 5 weeks (c).
callus was still present. Although cortical bone was not yet fully reconstructed, its quality seemed excellent (Fig. 2.5).

### 2.1.2.2 Histological Results

On the 14th day, examination of the slides revealed the following:

- Periosteal callus consisted of small free-standing trabeculae of new bone laid down upon the fibrous tissue. Tissue fibers defined the trajectories of the trabeculae. These trabeculae were already interconnected and had specific orientation patterns: at some distance from the fracture site, they were oriented perpendicular to the adjacent cortex, whereas at the fracture site, they were parallel to the long axis of the bone. A few islets of cartilage could be seen at the periphery of callus, sometimes creating a narrow bridge between the ends of the cortices.
- There was no sign of cortical bone resorption and no abnormal osteoclastic activity.
- There was excellent medullary vascularization, and many blood capillaries were over 0.2 mm in diameter. One striking finding was the presence of bone islets and trabeculae around the intramedullary nails.

To give an idea of the intensity of periosteal reaction, let’s just say that it doubled the diameter of the bone.
Shaft (including both cortices). Mean diameter of the diaphysis was 6 mm, of the medullary cavity was 3.2 mm, of each intramedullary nail was 1 mm, and that of the periosteal callus was 11.5 mm.

The third week (Fig. 2.6):

- Peripherally, bone trabeculae got thicker and numerous interconnections were observed. Intense osteoblastic activity was characterized by a large number of osteoid rims and fence-like cell arrangement.
- As regards cortices, neither resorption nor reconstruction was noted: bone ends did not seem to take part in the repair process.
- On the other hand, endosteal callus trabeculae extended from both ends of the fragments and formed a small bridge.

At the end of the first month, hard callus maturation was still going on via perfectly interconnected primary bone trabeculae. Intense osteoblastic activity was observed, whereas no osteoclastic resorption seemed to take place.

After 6 weeks (Fig. 2.7):

- There was no real change in endosteal and periosteal ossification, and in any case, no remodeling. And yet, when examined under polarized light, bone trabeculae had a pseudo-lamellar appearance characteristic of bone repair.
- Callus was peripherally delimited by a thin layer of lamellar bone that encompassed the entire fracture site.
- Callus, consisting of small, highly interconnected trabeculae began spanning over the fracture gap. It was not yet remodeling but simple primary ossification, a kind of “osseous anastomosis” (Fig. 2.8).

At 3 months, peripheral resorption was initiated, even though the osteoblastic activity still predominated.
2.2 Combined FIN/Ilizarov Method for Bone Lengthening in Dogs

Based on our extensive experience with the Ilizarov lengthening method, we have demonstrated that one of its fundamentals is preservation of periosteum and intramedullary circulation. Furthermore, quality of the regenerate depends on the lengthening rate, which can be individualized [2]. Automatic high-frequency lengthening and compression of the regenerate immediately after the lengthening period provide optimal conditions for tissue regeneration, and result in significant reduction of the external fixation period [3]. Works have been done to demonstrate the prominent role of periosteum in distraction osteogenesis [4, 5]. Intramedullary nailing provides a strong elastic frame, which enhances the formation of periosteal callus. Additionally, as the two intramedullary nails do not completely fill the medullary cavity, endosteal callus formation is not inhibited. We have worked on the FIN concept to ensure compatibility with the Ilizarov method for limb lengthening. The following study conducted in dogs allows to better understand our philosophy, and evaluate all the benefits of this combined method.

2.2.1 Materials and Methods

This study was conducted in 14 dogs of various breeds, aged 1 to 4 years, with an average weight of 18.8 kg. Mean length of tibia was 187 mm. The Ilizarov fixator used consisted of two distal rings and two proximal three-quarter rings, connected by threaded rods. Both percutaneous osteotomy of the fibula and osteoclasis of the tibia were performed in the middle third of the diaphysis. The FIN construct used two 1.5 mm nails with opposing curves (Fig. 2.9). Both nails were sharply contoured, and their tips bent to 30–40° over a length of 2–3 mm. Their initial curves were identical, with apex located in the midsection. Both nails had blunt tips. Two slightly oblique entry holes were made with an awl in the superior portion of the proximal metaphysis. The first nail was hand pushed into the medullary canal, then across the osteoclasis and down to the distal metaphysis, as far as possible into the cancellous bone. The second nail was inserted in the same manner, on the opposite side of the bone. The final

2.1.3 Conclusion

With FIN, fracture healing occurs via an initial fibrous tissue on which trabeculae of new bone are laid down to form periosteal callus (external callus). The cartilage callus phase is not mandatory; actually, it is often bypassed. The next stage of bone repair is the formation of endosteal callus and medullary ossification along the intramedullary nails. Then, bridging external callus forms to establish contact between the fragment ends, but the strong lamellar bone is still not involved in remodeling.

The chief advantage of FIN is to promote rapid healing while preserving the patency of the medullary canal, thanks to the presence of the intramedullary nails, which further minimize the risk of mid-term recurrent fracture.
Fig. 2.9 Radiograph of the right tibia (dog). Tibial lengthening by combined Ilizarov/FIN: (a) Ilizarov fixator and intramedullary nails in place, osteoclasis of the tibia; (b) X-ray taken after 21 days of lengthening; (c) X-ray taken after 28 days of lengthening (end of lengthening period). Note the intense and extensive periosteal reaction, and a growth zone with numerous bone trabeculae. Thirty millimeter lengthening; (d) Complete healing achieved after 14 days of external fixation, external fixator removed.
construct consisted of two nails with opposing curves positioned in the same plane. The free ends (trailing ends) of the nails were cut relatively short and bent to about 45–60° to prevent nail migration during distraction. The skin was closed in one layer. Distraction was initiated on the fifth day in all dogs (Fig. 2.9). Duration of lengthening was 28 days. Mean distraction rate was 1 mm/day (in four steps) (Table 2.1). However, as control X-rays showed extensive bone regenerate, the distraction speed had to be increased at d 8 in 4 dogs, d 15 in 3, and d 21 in 1. Early healing occurred twice after about 21 days of lengthening, and twice after about 28 days: in two cases, distraction resulted in fracture of the regenerate that had already consolidated (Fig. 2.10), whereas in the other two cases, the newly regenerated bone was already very strong. The 28-day lengthening period was followed by the external fixation period. The external fixator was removed after 15 days (sixth week) in eight dogs and 30 days (eighth week) in four. All the dogs could bear weight right after removal of the external fixator without any limb protection.

Results were evaluated based on the radiographic appearance of the regenerate. Control X-rays were performed on a weekly basis throughout the distraction period, and thereafter, at 45 days, 60 days, and after removal of the intramedullary nails. Arteriographies were performed in some dogs after sacrifice: at d 5, 39, and 63. Additionally, bone regenerates were histologically studied.

### 2.2.2 Results

Radiological changes indicated intense and extensive bone regeneration, which forced us to increase the distraction speed in some dogs. Newly formed bone was visible on radiographs after about 7 days of lengthening. At this stage, the regenerate had an inhomogeneous structure with localized areas of increased bone density. Extensive periosteal reaction (21.6 mm long, 0.5–2.0 mm thick) could be noted along the bone fragments. At 2 weeks, the regenerate was well structured and filled completely the interfragmentary gap. The growth zone contained numerous bone trabeculae. Periosteal reaction was 24–26 mm long and 2–3 mm thick. The regenerate was larger than the tibia. After about 15 days of fixation (d 48), the regenerate was completely consolidated in all the animals. Cortical bone was reconstructed. Continuity of three or four cortices was reestablished along the regenerate. The growth zone had disappeared. A denser periosteal reaction was noted. After about 30 days of fixation (d 63), the medullary canal was already formed in three out of four dogs. No fracture or deformity occurred after removal of the external fixator because the regenerates

### Table 2.1 Duration of lengthening and external fixation

<table>
<thead>
<tr>
<th>Period</th>
<th>Osteoclastis, ilizarov + FIN</th>
<th>Distraction (lengthening)</th>
<th>External fixation</th>
<th>Removal of external fixator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td>Day 0</td>
<td>Days 5–33</td>
<td>Days 34–49 = 6 dogs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 49 = 6 dogs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 63 = 8 dogs</td>
<td></td>
</tr>
</tbody>
</table>
had already consolidated, and also because the bones were protected by FIN.

After 15 days of external fixation, histology showed cortical continuity, fully interconnected cancellous trabeculae, and disappearance of the fibrous layer surrounding the new bone (Fig. 2.11a). As a matter of fact, consolidation took place during the fixation period and lasted 2 weeks.

Thirty days after removal of the external fixator, the cortices were thicker. Remodeling of the medullary canal was under way. We were happy to note extensive tissue regeneration along the intramedullary nail (Fig. 2.11b).

This structure can be compared to a stainless steel lead pencil.

Arteriographies performed at the initiation of lengthening, after 6 days of external fixation, and immediately after removal of the intramedullary nails (Figs. 2.12a and 2.12b), showed that the medullary artery had remained patent all the time.

Lastly, no implant migration or skin problems occurred. We found that proper nail contouring ensured stability of bone fragments during lengthening.

2.2.3 Discussion

The Ilizarov lengthening method has revolutionized the biology of bone and bone growth. Preservation of bone environment, periosteum, and particularly, the medullary vascularization, respect of the biological rate of bone growth, use of automatic high-frequency lengthening, preservation of stability and elasticity (provided by the rings): all this works together to provide good to excellent tissue regeneration [3]. The more stable the lengthening site is, the faster it will heal. Although Ilizarov claimed that bone marrow played a major part in new bone formation, a certain number of works that tried to demonstrate the paramount qualitative role of periosteum in distraction osteogenesis have been published [4, 5].

FIN has a proven track record of over 25 years of effective treatment of fractures in childhood based on animal experimentation [1] and above all, on the outstanding experience of the Department of Pediatric Orthopedics, Clinique Chirurgicale, Nancy (France). According to these works, FIN provides a strong elastic frame that enhances the biological effect of redistribution
2.2 Combined FIN/Iizarov Method for Bone Lengthening in Dogs

of blood flow to the periosteal structures through cortical canals, thus stimulating formation of periosteal callus. FIN is a semi-rigid elastic nailing system, which allows for cyclic micro-scale plastic deformation that is most beneficial to healing. Additionally, as the two intramedullary nails do not completely fill the medullary cavity, endosteal callus formation is not inhibited.

We had the idea to combine both elastic systems, Iizarov and FIN, for limb lengthening [6]. Our animal experiments prove that contoured intramedullary nails do not inhibit endosteal bone formation. On the contrary, despite partial destruction of the bone marrow, the preserved intramedullary circulation stimulates tissue regeneration to such an extent that it becomes necessary to increase the distraction speed to avoid premature consolidation of the regenerate during lengthening.

The biological effect of redistribution of intramedullary blood flow to the periosteal structures stimulates formation of periosteal callus, resulting in extensive

Fig. 2.11 Histologic sections (tibia – dog): (a) specimen at d 49 (fixator removed), cortices were present along the regenerate and continuity was re-established. Growth zone was no longer visible; (b) specimen at d 88, 25 days after removal of the external fixator, intramedullary nails were removed just before sacrifice. Regenerate consisted of cortical and cancellous bone tissue. The medullary canal was patent. Ossification was present along the intramedullary nails

Fig. 2.12 Arteriography: the medullary artery was patent (tibia – dog). (a) Arteriography (AP and lateral) of specimen after removal of the intramedullary nails on the 6th day of the fixation period (d 39); (b) arteriography (AP and lateral) after 30 days of fixation (d 63)
periosteal reaction, both along the bone fragments and at the diastasis. When combined Ilizarov/FIN is used, the periosteal reaction is indicative of active tissue regeneration rather than instability of bone fragments.

FIN provides increased stability at the diastasis by resisting translation motion (essentially) in the plane of the nails. Gradual stretching or sliding of the intramedullary nails through the regenerate during lengthening likely enhances the regeneration process. However, the mechanism of biological stimulation of endosteal bone formation remains unexplained. Controlled bone marrow irritation by an intramedullary nail is known to produce localized new bone formation [1]. This has been confirmed in animals, where intramedullary nails positioned at the periphery of the regenerate and gradually pulled have shown to accelerate the formation of new bone [7].

2.2.4 Conclusion

FIN can be used conjointly with external fixation for bone lengthening. Combined use of these two methods allows to stimulate both endosteal and periosteal bone formation. FIN improves stability of the bone fragments at the diastasis, and does not inhibit intramedullary circulation. In bone lengthening, FIN is the only internal fixation method that provides the same optimal conditions for bone regeneration as the Ilizarov method. This is why combined Ilizarov/FIN yields such a good outcome. The results of this experimental study have been, in our department at Kurgan, a determining factor for the use of combined Ilizarov/ FIN method in bone lengthening and correction of bone deformities in patients with limb length discrepancy (LLD) and skeletal pathologies such as familial hypophosphatemic rickets.

References

Flexible Intramedullary Nailing in Children
The Nancy University Manual
Lascombes, P.
2010, XVIII, 317 p., Hardcover
ISBN: 978-3-642-03030-7