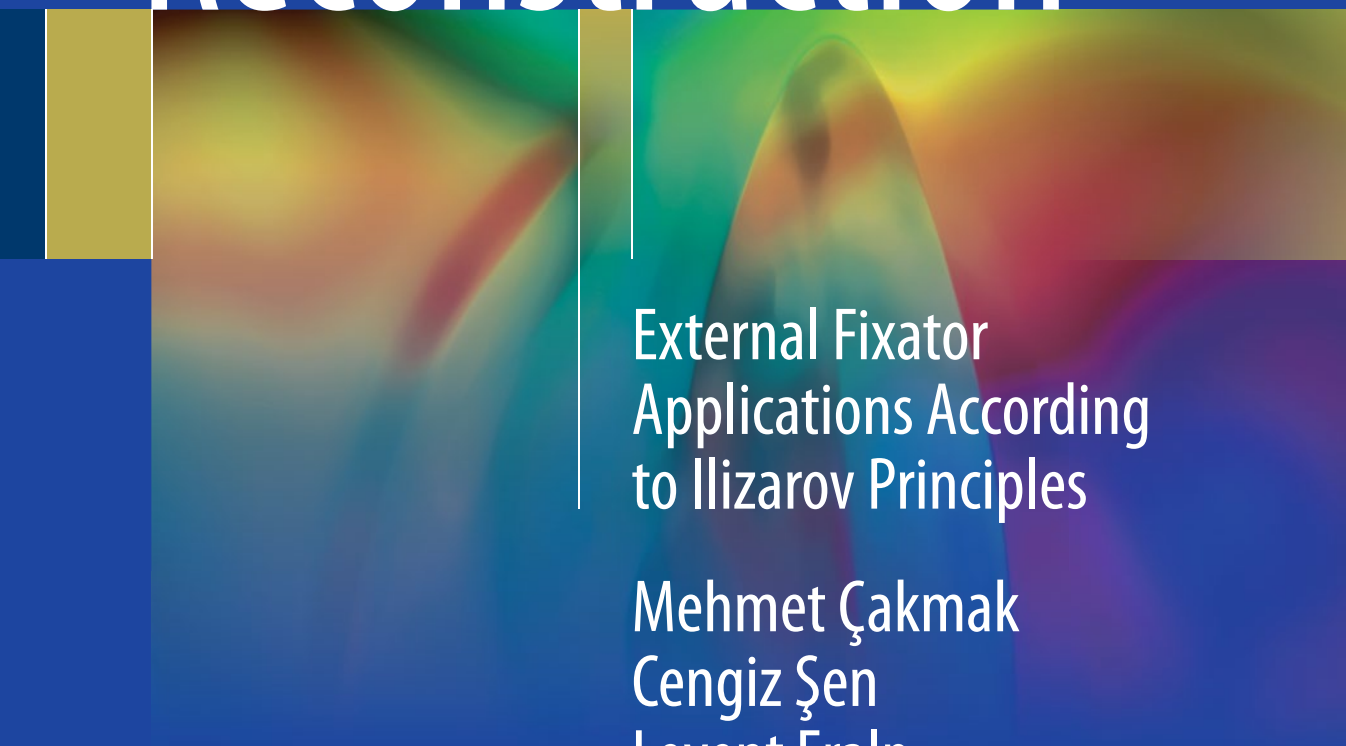
Basic Techniques for Extremity Reconstruction



External Fixator Applications According to Ilizarov Principles

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Foreword

Turkey sits at the crossroads of the East and West, between Asia and Europe. The Ilizarov technique is a product of technology that developed in Asia and migrated to Europe. It is therefore only fitting that a major work on the Ilizarov method be compiled by the person who introduced the Ilizarov method to Turkey. I first met Professor Mehmet Çakmak in 1992 in Pakistan when we were both visiting professors. Professor Ilizarov had just died so that this was a solemn occasion for our first meeting. I had the privilege to be Dr. Mehmet Çakmak's guest in Turkey. He has remained the first pioneer of this method in Turkey and has stimulated many of his residents to pursue this field of study. One of his most promising disciples is Dr. Mehmet Kocaoglu who was my first Turkish fellow. It is through this friendship and collegiality that a great cooperation has remained between myself and the Turkish orthopedic specialists in this field. This cross-fertilization has spawned innovation from across the Bosporus that has contributed significantly to the world knowledge on all aspects of Ilizarov technology including limb lengthening, deformity correction, treatment of nonunions, bone defects, and osteomyelitis and the understanding and management of the complications of such complex treatments. I wish to congratulate Professor Mehmet Çakmak and his many coeditors and authors for this significant achievement, which stands as another monument to Professor Ilizarov's revolution in orthopedics more than 30 years since his methodology was introduced to the West. The reader will find this tome a great reference source to the most up-to-date understanding and techniques associated with the Ilizarov method and device.

Florida, USA — Dror Paley, MD, FRCSC

Preface from the Editorial Board

Dr. Gavril Abramovich Ilizarov coined the term "distraction osteogenesis" in the 1950s, and most diseases that could not previously be treated or ended with failure were treated with the method he developed. For a long time, the method was used only for acute fractures or nonunions. After Russia, the new method was first used in Italy and then in other European countries and the United States. The method was appreciated by physicians in time. "The Ilizarov philosophy" has been used more frequently in orthopedics, particularly after the considerable contributions of Dror Paley in the United States in the 1990s. The book entitled *Principles of Deformity Correction* written by Dr. Paley has been widely accepted in orthopedics and successfully used in the treatment of many patients.

The first textbook in Turkey, *Ilizarov Surgery and Its Principles*, was published in 1999 with contributions of experienced colleagues after they performed the method in their clinics. In 2004, the 3rd International ASAMI Congress was held in Turkey, at which there were participants from all over the world. We published books in Turkish *Ilizarov in Trauma* and then *Ilizarov in Deformity Surgery* after about 30 years of experience using the Ilizarov technique with the aim of contributing to the education of colleagues who were willing to perform the method. We wanted to publish a book in English that synthesizes the information of the latter books and offers a methodologic approach to all basic and current information about Ilizarov surgery. We believe that the correct performance of deformity analysis principles is the core and essential element of this treatment. We think that Ilizarov applications are important weapons in a surgeon's armory and sometimes the primary choice in traumatology. In this book, you will find examples of computer-assisted fixator applications, which are frequently used in Turkey and around the world. You will also find information about new methods developed by some of our creative colleagues. We know that young colleagues will find the answers to all questions in their minds.

We want to thank and express our gratitude to our colleagues who spent their valuable time preparing the chapters of the book, David Francis Chapman and Kadriye Gümüş from the Publication Support Department in Istanbul University for their support in translating and editing the book, Özge Papakcı Aydın for her contribution to some of the illustrations, and Erol Al for his endless rigorous work as the secretary of the Ilizarov patient archive.

We hope this book will have a humble contribution to our colleagues worldwide who are willing to devote their lives to Ilizarov surgery and continuing the work in this area.

The Editors

Preface

I started my resident training in 1973 in Istanbul University, Orthopedics and Traumatology Clinic. The biomechanical rules and principles in orthopedics were very different in the 1980s than they are today when I first became the chief resident in the same clinic. Communication and information exchanges were not easy either. It was really hard to produce information and spread it around the world. I have always felt lucky for being a member of this well-established orthopedics clinic. I was just an apprentice in the challenging nature of orthopedics; then I became a professor who was operating and implementing techniques for the first time and teaching at the same time.

In 1983, I read in a newspaper that a physician in Russia had successfully performed a 30-cm extremity lengthening without a need of an operation. When I decided to investigate the news, the philosophy was very new in the world, and all the articles were written in Russian. We brought the articles to Turkey and had them translated. Ultimately, we had met "distraction osteogenesis." Our journey started with our first operation in 1984, meeting Ilizarov in person in 1988 and attending international symposium in limb lengthening in Pakistan in 1992, and with the organization of the third international ASAMI meeting in 2004. Today the journey continues with the organization of meetings and congresses and with the academic studies of our fellow colleagues.

I will be grateful to present my thanks to my colleagues who teach the Ilizarov philosophy and treatment methods for their contribution in this book. They immediately supported me without any hesitation when I shared my ideas about the project. They contributed with their knowledge and experiences from all over the country. This book has arisen when all the knowledge and Ilizarov's basic principles and methods were gathered together. The aim of this book is to convey this knowledge and experience to the next generation because these are secret weapons for each orthopedic physician and sometimes it is a way of life. Despite all the recent developments and technology, Ilizarov's circular external fixator will always continue performing miracles, such as it did on the first day.

I will be grateful to present my thanks to my dear wife for her support throughout my life, to my distinguished professors who educated me, to all authors who shared the same excitement, and to the editorial team who successfully managed and organized this challenging process.

Istanbul, Turkey — Mehmet Çakmak

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Part I

External Fixator Applications for Complex Fractures

History and Phylosophy of Ilizarov's Method

1

Levent Eralp

External fixation was first used by Hippocrates around 2500 years ago for the treatment of tibia fractures [1]. Jean Francois Malgaigne described a fixator device and named it "Griffe" in 1840. In 1843, he used the device to hold the fragments of a tibia [2, 15]. In 1897 Clayton Parkhill invented a modern unilateral fixator known as a "bone clamp" and published the first series of 14 patients treated with external fixation [3]. The first biomechanically tested fixator used for fracture treatment was invented by Italian surgeon Della Mano. The device was the first structural example of rings and wires [4]. Various types of external fixators were used during the First and Second World Wars for treating open or closed fractures with or without bone defects.

In the early 1950s, a Russian physician named Gavril Abramovich Ilizarov invented an external fixator. He patented his device in 1951 while he was working in the General Surgery Department of the Kurgan Regional Hospital. Initially, he used this device for compression at fracture sites. Thereafter, he observed some patients were making distractions instead of compressions erroneously and yet there was still new bone formation. Consequently, he started working on a distraction method for osteogenesis [5, 6].

He studied distraction osteogenesis in animal models. Because of the strict political structure of the Soviet Union, his work remained unpublished internationally until 1972. The Ilizarov method reached high national attention with the treatment of nonunion of Valeriy Brumel in 1968, the Soviet gold medal high Jumper. Valeriy Brumel was an Olympic champion and a longtime world record holder in the men's high jump. He injured his right foot in a motorcycle accident. Before he was accepted to Kurgan, he was unsuccessfully treated in various clinics [7, 12, 17].

After attracting the attention of his country, Ilizarov appeared in Western press with the successful treatment of infected tibia pseudarthrosis of Carlo Mauri, an Italian mountain climber, explorer, and journalist. After 10 years of unsuccessful treatment, Mauri heard about Ilizarov and went to Kurgan in November 1977. Ilizarov treated him in 6 months and Mauri called him the "Michelangelo of Orthopedics" [8, 16]. Because of the amazing recovery of his leg, Italian orthopedic surgeons invited Ilizarov as a guest speaker to the 22th AO Italy conference in Bellagio in June 1981. Under the chairmanship of Professor Roberto Cattaneo, Chief of Orthopedics and Traumatology of Lecco General Hospital, he gave three lectures about the treatment of open fractures and posttraumatic osteomyelitis and bone lengthening, and this was the first time Ilizarov lectured outside his motherland.

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After the meeting, Italian orthopedic surgeon Prof. R. Cattaneo and his associates, A. Villa, M. Catagni, and L. Tentori, started experimental trials with the set that was donated by Ilizarov to Lecco General Hospital. In 1982, the Association for the Study and Application of the Methods of Ilizarov (ASAMI) was founded in Lecco, Italy. After Prof. Ilizarov moved to the new building in Kurgan named The Russian Ilizarov Scientific Center for Restorative Traumatology and Orthopedics (RISC RTO) as a chief scientist, an Italian delegation of surgery consisting of professors A. Bianchi Maiocchi, G. B. Benedetti, A. Villa, and M.A. Catagni visited him in Kurgan in April 1982 (Fig. 1.1).

The RISC had 1200 beds, 12 operation rooms, 15 experiment labs, and an experimental animal laboratory. The knowledge about distraction osteogenesis was enhanced in the following years because of the integrated work between Russian and Italian surgeons (Fig. 1.2).

ASAMI started courses named "Theoretical and Practical Application of Ilizarov's Method" in Lecco, June 1983. Ilizarov directed the first course with his assistant Dr. V.I. Schevstov with the attendance of more than 300 surgeons from all over the world.

In September 1983, the First International Transosseous Osteosynthesis Symposium was organized in Kurgan. More than 800 orthopedic surgeons attended the meeting from outside the USSR. This meeting introduced Prof. Ilizarov to the whole world, and he subsequently supervised meetings and gave lectures in courses organized in Spain, France, Switzerland, Portugal, Greece, Brazil, and the United States of America (USA) between 1983 and 1985. He gave a "professorial lecture" on the "treatment of nonunion" on the last day of second instructional course of Ilizarov's method in Bergamo, Italy, in front of the president of SICOT and the founder of AO International, Prof. Maurice Müller. After the method had been accepted in the USA in the late 1980s, the whole world used the method for specific fields of orthopedics (Fig. 1.3).

From North America, Sarmiento, MacEwen, and Victor Frankel were the first surgeons who

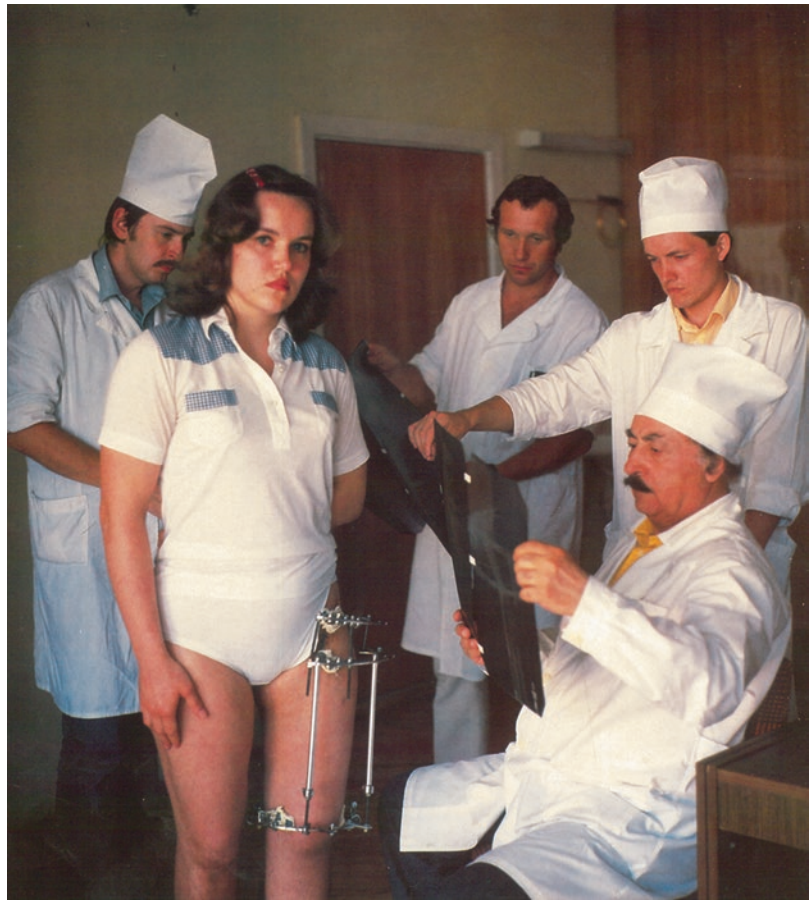

Fig. 1.1 Prof. Dr. G. A. Ilizarov examining a patient (From the International Advertisement Brochure of Kurgan Research Institute of Experimental and Clinical Orthopedics and Traumatology, 1989)

were introduced with this technique in 1983 and 1984. Dr. James Aronson learned the technique from Prof. R. Bombelli in 1984, Lecco. While Bombellini was a visiting Professor in Toronto, Dr. Dror Paley, a senior resident in orthopedic surgery heard about the method. In 1985, Paley visited Lecco for 2 weeks, and because of the slow learning curve, he decided to do a fellowship for 6 months in Lecco, Bergamo, and Kurgan. After learning the technique in detail, he clinically applied the technique first in Toronto and then in Baltimore, Maryland, in 1987.

Fig. 1.2 RF Ministry of Healthcare (2015), The Russian Ilizarov Scientific Center for restorative traumatology and orthopedics [ONLINE]. Available at http://en.ilizarov.ru/index.php/about-center/center-today [Accessed 16 November 15]

Fig. 1.3 Ilizarov lecturing about his techniques (From the International Advertisement Brochure of Kurgan Research Institute of Experimental and Clinical Orthopedics and Traumatology, 1989)

Fig. 1.4 Prof. Dr. Mehmet Çakmak (*right*) was the first surgeon to use Ilizarov's technique and limb lengthening with circular external fixators in Turkey. Also in the photograph is Dr. Cerkez-Zade (*center*) and Dr. Schevstov (*left*)

In 1987 Dr. Paley and V. Frankel organized the first meeting with the attendance of Prof. Ilizarov, which was held in New York and the next year in Washington, D.C. Dr. Stuart Green from Los Angeles translated all the work of Ilizarov with his approval and trust for Western countries to use and published the entire works in Clinical Orthopedics and Related Research in 1989 and Ilizarov's book in 1992 [9, 13].

After the method was accepted worldwide and its use began, many clinical and biomechanical trials and experiments were done. The system was improved in the 1990s with additional parts and modifications and became more modular and useful. Superposition problems were solved in imagining with the use of carbon fiber rings [14].

In Turkey, external fixators were first used by Dr. Orhan Aslanoğlu for limb lengthening procedures. Dr. Orhan Girgin used his own designed fixator for tibia lengthening in Numune Hospital, Ankara, in 1978. Although he failed in the first procedures, he revised his device and started lengthening again in 1979.

The history of the application of the Ilizarov's method in our clinic has been presented as a lecture by Prof. Dr. Mehmet Çakmak who was the first surgeon to use this technique. I prefer to continue with his own words for describing our clinic's story with this epic discovery (Fig. 1.4).

> I was chief resident in 1980 and the whole world had been using compression for union of the fracture site. Limb lengthening had been performing very rarely and maximum amount of the lengthening couldn't have been more than 2 or 3 centimeters. Plates had been commonly used in those days, and fixation after osteotomy and traction was the ultimate solution. Until 1983, limb lengthening procedures had been performed by the method of shortening osteotomy or epiphysiodesis. However, these procedures were planned for healthy limbs and parents or patients were hardly accepting these procedures.
>
> Ilizarov showed us that some of the knowledge popular in those days could have been wrong or insufficient and against the physiology of the human body. The philosophy of the Ilizarov had been learned by Italian Orthopedic Surgeons and with the treatment of the tibia pseudarthrosis of Carlo Mauri, Italian journalist and climber. That case was the gate for the knowledge and Europe had been finally informed about this new innovation.
>
> Two years after the Italian surgeons in 1983, Turkey was the second stop for this knowledge, and I was very curious about this new technique and was determined to learn it. In 1983 I heard about this "magician" in a newspaper. This newspaper article was saying that a man called Ilizarov in Russia were lengthened a patient's limb by about 30 cm without bleeding. I can say that this news

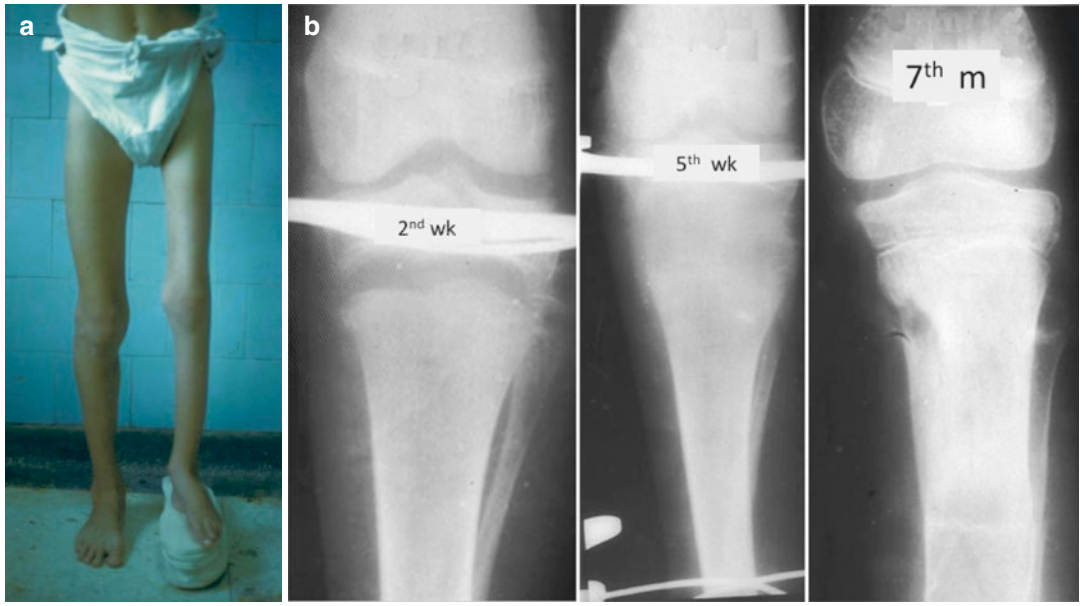

Fig. 1.5 The first patient who underwent a lengthening procedure in our clinic. Clinical photo and follow up X-rays

was more likely to be fake. But I followed the source and because of the empty literature I requested the scientific publishing about this technique from the USA. With the help of our nurses who knew Russian, my colleague Dr. Kocaoğlu and I finally got the translated documents and articles.

Distraction osteogenesis was the main subject and some illustrations had been in the papers. We decided to prepare the parts after getting g deeper in this subject. The first experimental studies were performed using amputated materials of patients, and some biomechanical studies had been applied [10, 11].

Successful results encouraged us to apply this method in a human subject. Our first patient was an adolescent boy with significant shortness in his left limb. His father trusted us and we informed them about the procedure.

The patients X-rays can be seen in the figures below and this patient zero (as we call him) gladly volunteered for more clinical photos 22 years after the procedure (Figs. 1.5 and 1.6).

There was a significant risk about arrest of the growth plate with the method of distraction epiphysiolysis. And the method could be used until the growth plate is closed. Callotasis was the ultimate innovation after work started on this part of the orthopedics. Thus, we performed distraction epiphysiolysis on a patient whose growth plate we thought was still open. But his growth plate was closed and the K-wires started to bend after seven days of distraction. We realized that we had mistakenly prepared using old X-rays before surgery. In other words, we were unaware of the discovery of this method by the time we started to use it in our patients in 1987.

We heard that Ilizarov himself had started to visit various countries for lectures and he was visiting Turkey in 1989 because of one of his patients. Thankfully, he accepted our invitation and the CEO of the Enka Corporation Şarık Tara sponsored the conference. He showed very interesting cases, and we were deeply surprised after we listened to his presentation (Fig. 1.7).

I met with Dr. Paley in the conference held in Pakistan in 1992. Dr. Paley had contributed mathematical aspects to deformity surgery. I had the chance to invite them to Turkey as well. At same time, Schevstov invited me to Kurgan, Russia. My visit to Kurgan was also very inspiring and made me realize that this scientific work and methods were new and magnificent innovations in the field of orthopedics and were all worth spending a lifetime.

Routine lengthening procedures started after I visited the RISC, Kurgan, in 1993 with Dr. Kocaoğlu and Dr. Kılıçoğlu. Dr. Ilizarov had recently passed away and Dr. Schevstov was the president of the institute (Figs. 1.8 and 1.9). After 1991, we published a number of studies about Ilizarov's method. In 1994 at the annual Professor Akif Şakir Şakar Memorial Days (founder of the Orthopedics Department of Istanbul University), under the chairmanship of Dr. Schevstov and Dr.

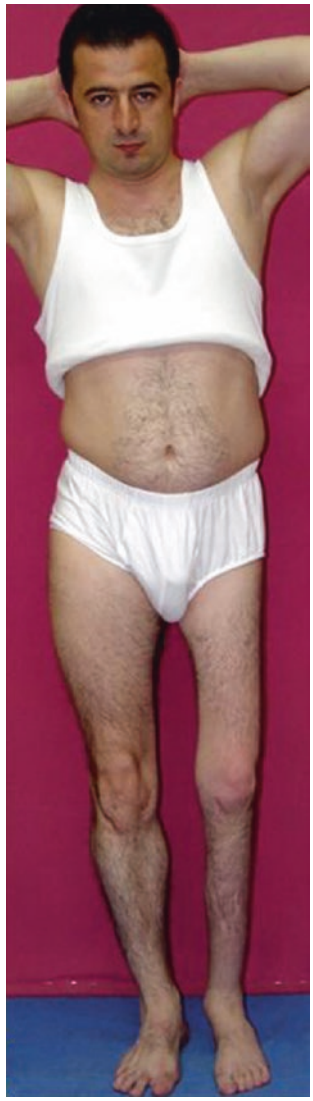

Fig. 1.6 22 years after the first lengthening procedure, clinical photo of "patient zero"

Cherkez-Zhade, with more than 300 participants, the methods and studies from all over the world were discussed. Instructional courses for Ilizarov's method had started in Çukurova University, Adana, and courses have been organized every year since then. There has been an active Ilizarov Polyclinic and Ilızarov Archive since 1995 in Istanbul University Orthopedics and Traumatology Department, which includes more than 5000 cases.

The Turkish ASAMI was established in 1999 and organizes postgraduate courses that help our young fellows to learn this knowledge. They lecture all over the country, and some of their work has reached around the world and carried this flag to the future. Our hope for our young colleagues is to be open to new ideas and keep imagining.

Fig. 1.7 Ilizarov's only presentation in Turkey, in 1989, Dr. Mehmet Çakmak (*left*) and Prof. Gavril A. Ilizarov (*center*) and Russian interpreter (*right*)

Fig. 1.8 Prof. Dr. Mehmet Çakmak with the statue of Ilizarov

Fig. 1.9 Prof. Dr. Mehmet Çakmak with Dr. Schevstov

Photo from 3rd Asami Meeting held in Istanbul, 2004 (From left to right; Dr. Levent Eralp, Dr. Mahir Gülşen, Dr. Mehmet Çakmak, Dr. Maurizio Angelo Catagni, Dr. Mehmet Kocaoğlu)

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The Histology and Biology of Distraction Osteogenesis

2

Vecihi Kırdemir

Prof. Dr. Gavril Abramovich Ilizarov, who had begun to design an external fixator in 1945, started his first fracture treatment with this equipment and had published his first results in 1950. Ilizarov had been using the external fixator for fracture treatment, and while he was treating a patient, instead of tightening the screws on the rods, he loosened them by mistake. With this mistake, he observed that there were also signs of union on the fracture line and callus formation in the distracted fracture line. In 1969, Ilizarov published results of his 10 years of work which was entitled "The course of compact bone reparative regeneration in distraction osteosynthesis under different conditions of bone fragment fixation (experimental study)." In his studies, he investigated distraction osteogenesis on 65 dogs and published his first conclusions [1–4].

After Ilizarov's mistake, orthopedic surgeons understood the following facts:

1. For fracture healing, compressive forces applied to the fracture line are not always needed.
2. The longitudinal bone growth does not originate from the cartilage cells in the growth plate. On the contrary, the growing bone originates from the bone tissue itself – the osteoprogenitor cells – in contact with the growth plate from above and below.
3. The significance of vascularization for fracture healing and bone growth.

First, external fixator devices are applied to the bone in the operating room. Thereafter, a low-energy osteotomy is performed to make a fracture line during the same session with stable fixation as Ilizarov described. After the operation, a 5-day waiting period for children and 7 days for adults, the osteotomy line is moved 1 mm/day via unscrewing the rods. This 1-mm elongation is achieved through four applications per day. Following osteotomy, new trabecular bone tissue develops between both bone surfaces based on this distraction. This process continues until the planned distraction distance is achieved (e.g., 10 days for 10 mm).

Newly formed tissue, rich in type I collagen, is a fibrous tissue that cannot be seen radiologically. The new repair tissue develops on the collagenous bridge formed between the two osteotomy surfaces. Collagen fibers and blood vessels are aligned parallel to the forces of distraction. Following full distraction, bone cells intensify as microcolonies and immediately become bone-like formations. This phase is called the consolidation phase.

The 10 % lengthening of muscle tissue due to the distraction of bone can be well tolerated;

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however, lengthening more than 30 % of the muscle length causes significant histopathological changes. Temporary histopathological changes are also seen in neurovascular structures due to distraction. Two months after the distraction, these temporary changes disappear. Tibial lengthening performed on rabbits also showed histopathological changes on the surface of the knee joint cartilage following a short period. It was observed that the growth of cartilage showed a decrease in the hypertrophic and proliferative zone thickness [2, 3].

Ilizarov explained the guidelines for bone lengthening between 1990 and 1995, according to the principles of histology and physiology in this manner [2].

E. Donnall Thomas received the Nobel Prize in the field of medicine for hematopoietic stem cell transplantation in 1990 [5]. In 2001, after discovery of key regulators in the cell cycle by Tim Hunt and Paul Nurse, information pertaining to the healing of fractures was again reevaluated [6]. In 2012, the Nobel Prize in the field of medicine was given to Sir John Bertrand Gurdon from England and Shinya Yamanaka from Japan for demonstrating that fully differentiated skin fibroblasts could be transformed into stem cells by reprogramming [7].

With these studies of D. Thomas, T. Hunt, P. Nurse, J. Gurdon, and S. Yamanaka, a new perspective has been brought in the field of histology and physiology. In today's practice, the clinical success in the healing of a fracture or an osteotomy is related to the integrity of the surrounding tissue and proper mechanical features of the bone that will be able to support possible weights. Stem cells are also needed for tissue healing. The cells that comprise bone tissue are called osteogenic progenitor cells. The formation of bone tissue, fracture healing, and the principles of distraction should be evaluated in enlightenment of the new literature which is about stem cells.

2.1 Definition of the Stem Cells

An organism develops by the proliferation and differentiation of the zygote, which is actually a stem cell. The zygote is a totipotent stem cell that has the ability to differentiate to any type of cell. However, during its existence, the features of the zygote to proliferate will be kept on, but the ability to differentiate will be restricted by the time.

Stem cells have two distinct features:

1. Proliferation
   (a) Clonality (embryonic stem cell (ESC), malignant cells, microorganism)
   (b) Self-renewal (adult stem cell (ASC))
2. Differentiation or potency

Proliferation and differentiation processes show some differences in embryonic cells and adult cells. For this reason, we divide stem cells into two groups: (1) embryonic stem cells (ESC) and (2) adult stem cells (ASC). In the embryo, each of the daughter cells formed by mitosis generally (clonality) contains both genetic and epigenetic characteristics of the principal stem cell (symmetric division) [if daughter cells have same epigenetic features between each other but different from mother cell, this is also called symmetric division] (Fig. 2.1). Sometimes one of the daughter cells contains the same genetic and epigenetic characteristic – as expected – but the other sibling has the same genetics but different epigenetic characteristics (asymmetric division). As a result of asymmetric division, this epigenetic difference reflects either as phenotypic difference or apoptosis.

In adults, stem cells want to keep their counts in constant to prevent becoming cancerous. For this reason, one of the daughter cells protects the same genetic and epigenetic characteristics (self-renewal), whereas the other daughter cell encompasses the genetic but different epigenetic characteristics. In asymmetric division, the daughter cell with the epigenetic differences preserves the ability to become a stem cell. However, in adults, the purpose is to prevent becoming cancerous and maintain constant counts, and the daughter cell with the different epigenetics generally loses the ability to become a stem cell and stays differentiated until the end of the differentiation process (Fig. 2.2, left column). Embryonic stem cells do not use self-renewal; they use symmetric or asymmetric division (apoptosis, inner cells, outer cells, endo-meso-ectodermal stem cells) (Fig. 2.2 right column).

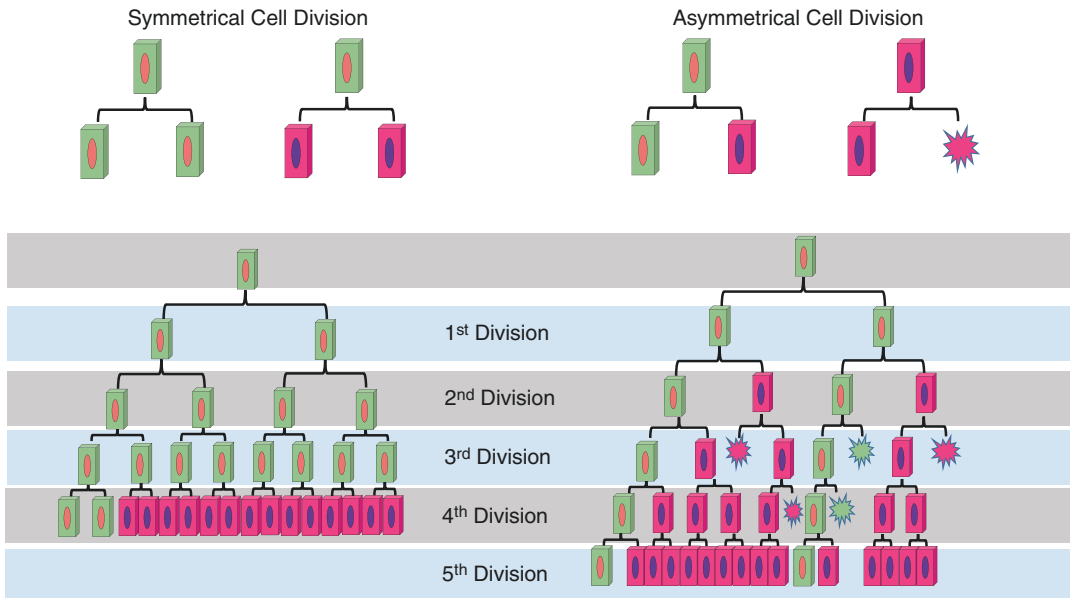

Fig. 2.1 Illustration of the symmetrical and asymmetrical division

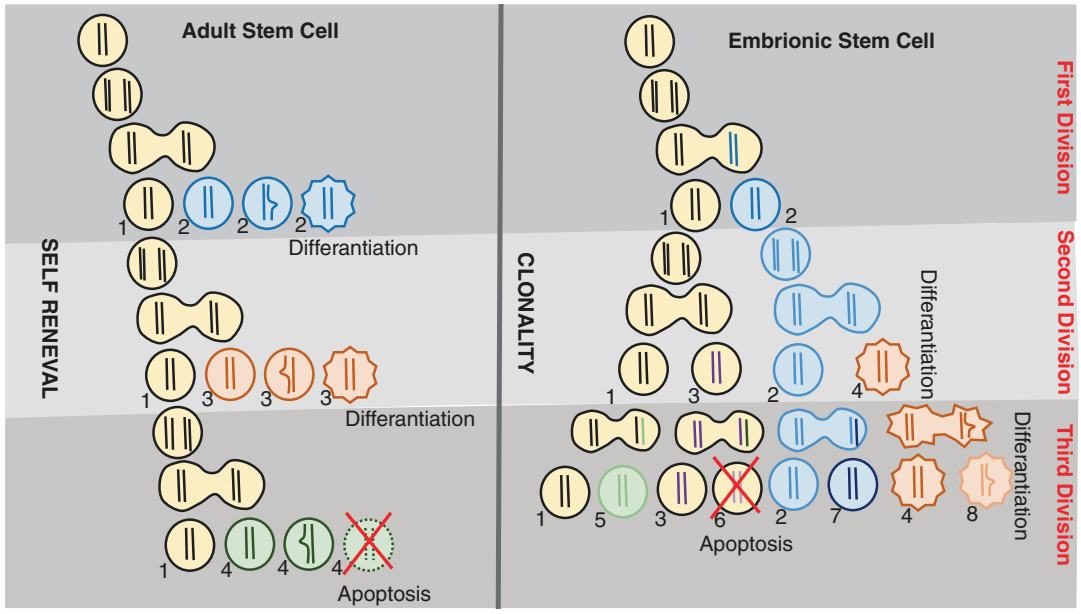

Fig. 2.2 Illustration of the proliferation and differentiation of the adult and embryonic stem cells

In adults and fetus following organogenesis phase, stem cells are found in microenvironments called "niches," e.g., bone marrow, pericytes in surrounding tissue of the vessels, hair follicles, intestinal epithelium, gonads, lymph nodes, satellite cells of the muscles, and peripheral blood.

2.1.1 Embryonic Stem Cell (ESC) and Bone Formation in the Embryo

Proliferation in the embryo is achieved by clonality. The principal cell transforms into two daughter cells by mitosis. It is believed that both of

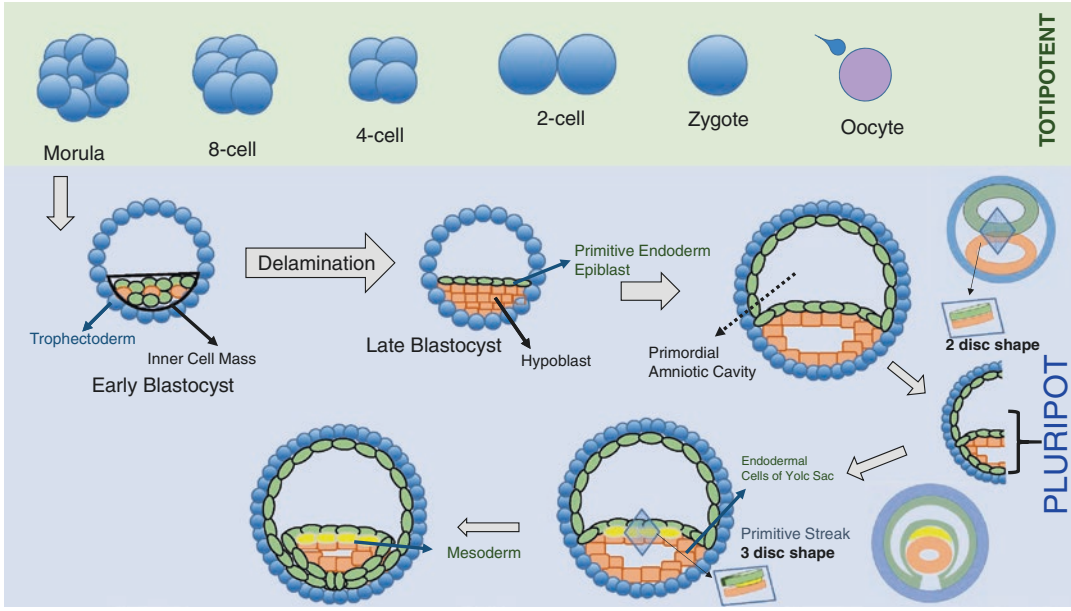

Fig. 2.3 Illustration of early embryonic differentiation

these daughter cells are capable of carrying the same characteristics (stem cell and same potency). The daughter cells can differ according to their potency (Fig. 2.2). This division can be *symmetrical* in which both of the cells carry the same characteristics or *asymmetrical* in which one of the daughter cells carries different epigenetic characteristics, while the other one does not (e.g., inner cell, outer cell, hypoblast, and epiblast formation).

Epigenetic transformation can result in three ways:

1. Change of potency, transformation into a new type of stem cell (hypoblast, epiblast) (totipotent-pluripotent)
2. Apoptosis – controlled cell death
3. Differentiation resulting in the final state [8]

In the embryo, the zygote proliferates by clonality until the 5th day (totipotent). On the 5th day, epigenetic differentiation takes place, and competency differs for developing inner cell mass (green-orange) and external cell (blue) trophectoderm layers. External cell groups are now only capable of producing cells for external tissues of the embryo, and inner cell mass is capable of developing the embryo (pluripotent = multipotent). External cell groups multiply asymmetrically and form the amniotic sac via apoptosis. Inner cell mass forms clusters and continues asymmetric division on the 7th day and differentiates into epiblasts and hypoblasts. The epiblasts form the ectodermal cell layers, whereas hypoblasts form the endodermal cell layers (Fig. 2.3) [8].

On the 9th day, some epiblasts are divided asymmetrically in order to differentiate into amnioblasts and extraembryonic mesoderm along with external cell layers [8].

Between the 9th and 16th days, epiblasts and hypoblasts continue to increase in number via symmetric and asymmetric divisions and produce two empty globes that consist of epithelial cells. The globe created by epiblasts (green globe) grows faster than the globe created by hypoblasts (orange globe). The orange globe will be surrounded by the green globe in order to create the hypoblastic cavity eventually (Fig. 2.3) [8].

The empty globe of the hypoblasts (orange circle in Fig. 2.3) first develops the temporary vitellus sac, and then the temporary vitellus sac transforms to the yolk sac. The amniotic sac is formed by epiblasts (green circle in Fig. 2.3). When the two globes are back to back, the interface

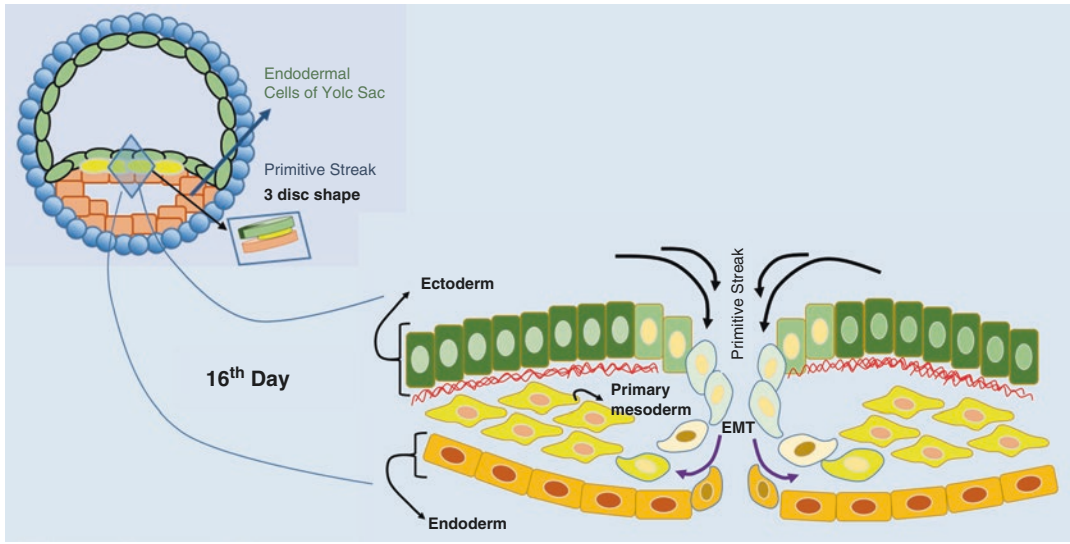

Fig. 2.4 Illustration of the embryonic development in the 16th day (epithelial-mesenchymal transition or EMT)

between the two globes forms an elliptical shape (fusion of both orange and green globes in Fig. 2.3). Epithelial contact areas of the globes are just like two discs on top of each other [8].

For surrounding the hypoblastic cavity, the disc belongs to the bigger globe cracks from the center toward the periphery at the 16th day (primitive streak) (Figs. 2.4 and 2.6). Around the 16th day, Wnt genes' signal pathway helps the streak to be formed in the ectodermal disc. By the help of this cleft, some epithelial cells from the upper disc migrate to the space between two discs.

Migration of these epithelial cells is called "epithelial-mesenchymal transition" (EMT). Theoretically this period can be referred by three discs as illustrated in Figs. 2.2 and 2.3 (ectoderm-mesoderm-endoderm). In order to form the mesenchymal disc, epithelial cells have to gain characteristics of mesenchymal cells by losing the ability of adhesion to each other and to the basal membrane. Along with the capability of migration, mesenchymal cells also have the ability to synthesize the surrounding extracellular matrix which cannot be created by epithelial cell layers [8, 9].

The stem cells which form two-disc shape resemble each other in epithelial features. However, in three-disc shape, stem cell differentiation begins. Stem cells in the middle disc have mesenchymal features. Three discs referring to embryonic germ layers are called ectoderm-mesoderm-endoderm. (Stem cells in these three layers are (1) embryonic ectodermal stem cells [EEcSCs], (2) embryonic endodermal stem cells [EEnSCs], and (3) embryonic mesenchymal stem cells [EMSCs]). These stem cells gain *multipotency* (9).

During the 16th day of the intrauterine phase, the formation of the mesenchyme tissue occurs by the migration of the stem cells whose phenotypes have changed based on the epigenetic changes of the stem cells in the ectoderm. The process of EMT and production of the mesenchymal stem cells (EMT type I) during the intrauterine phase are observed in adults during the repair of damaged tissue (EMT type II) and tumor metastases (EMT type III) [8].

On day 18, the edges of the neural plate start to thicken and lift upward forming the neural folds. The center of the neural plates remains grounded, allowing U-shaped neural groove to form. The neural groove gradually deepens as the neural folds become elevated, and ultimately the folds meet and coalesce in the middle line and convert the groove into a closed neural tube. This neural groove sets the boundary between the right and left sides of the embryo. The ectodermal wall forms the rudiment of the nervous system (Fig. 2.5).

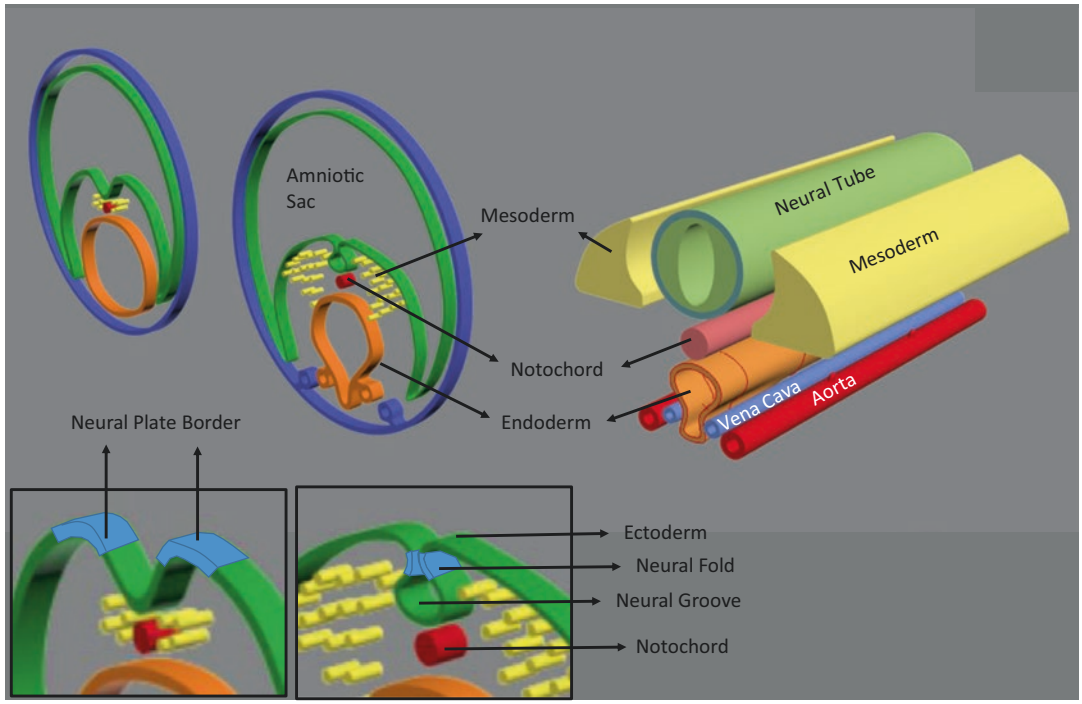

Fig. 2.5 Illustration of the neural tube development

The mesenchymal layer grows sideways and forward between the ectodermal and endodermal layers. Migrated cells which are positioned under the neural tube form the chordal process which transforms the "notochord" which is a primitive carina of the embryo between 19th and 21st days (Fig. 2.6). In the next stages of the fetal development, all germ layers will be supported by this structure. This rod is the skeleton holding the three layers stable and the first cartilage structure of the human embryo [8].

Because of the separate formation of the mesenchymal cells, unlike the epithelial cells, a matrix fills the intercellular space. This matrix facilitates the interaction with signal molecules. Signal molecules do not affect the epithelial and mesenchymal cells in the same way, and they can even change their own effect mechanism. The impact of the bone morphogenetic protein (BMP) is suppressed by the effect of Chordin and Noggin genes, and ESC differentiation leads toward the cartilage tissue. Vascular endothelial growth factor (VEGF) differentiates ectoderm and endoderm stem cells into vessel endothelium. These new vessels in the embryo cannot penetrate into the mesenchymal tissue because the cartilage matrix does not allow this action. However, cartilage cells continue to differentiate with the molecules produced by the Chordin and Noggin genes. This differantiation is not only due to the chemical effect (Chordin and Noggin), but by helping with the appropriate mechanical stimulation. The cartilage tissue at the tip of the anlage becomes dense and hypertrofic in midsecitons and might enter apoptosis. At the same time, apoptosis which takes place at the same structure keeps the tissues apart anatomically. The matrix has to be disintegrated enzymatically during this phase because phagocytic cells have not developed to disintegrate the matrix of cells yet. Metalloproteinase (MMPs) enzymes are used in this disintegration. Following completion of their purposes (segmentation and formation of joint gaps), their impact is stopped by other enzymes (tissue-inhibiting metalloproteinase [TIMPs]). Vascularization begins at the cavities formed after segmentation. Blood vessels in the embryo are created in two ways. The first way is differentiation of epithelial cells from endodermal

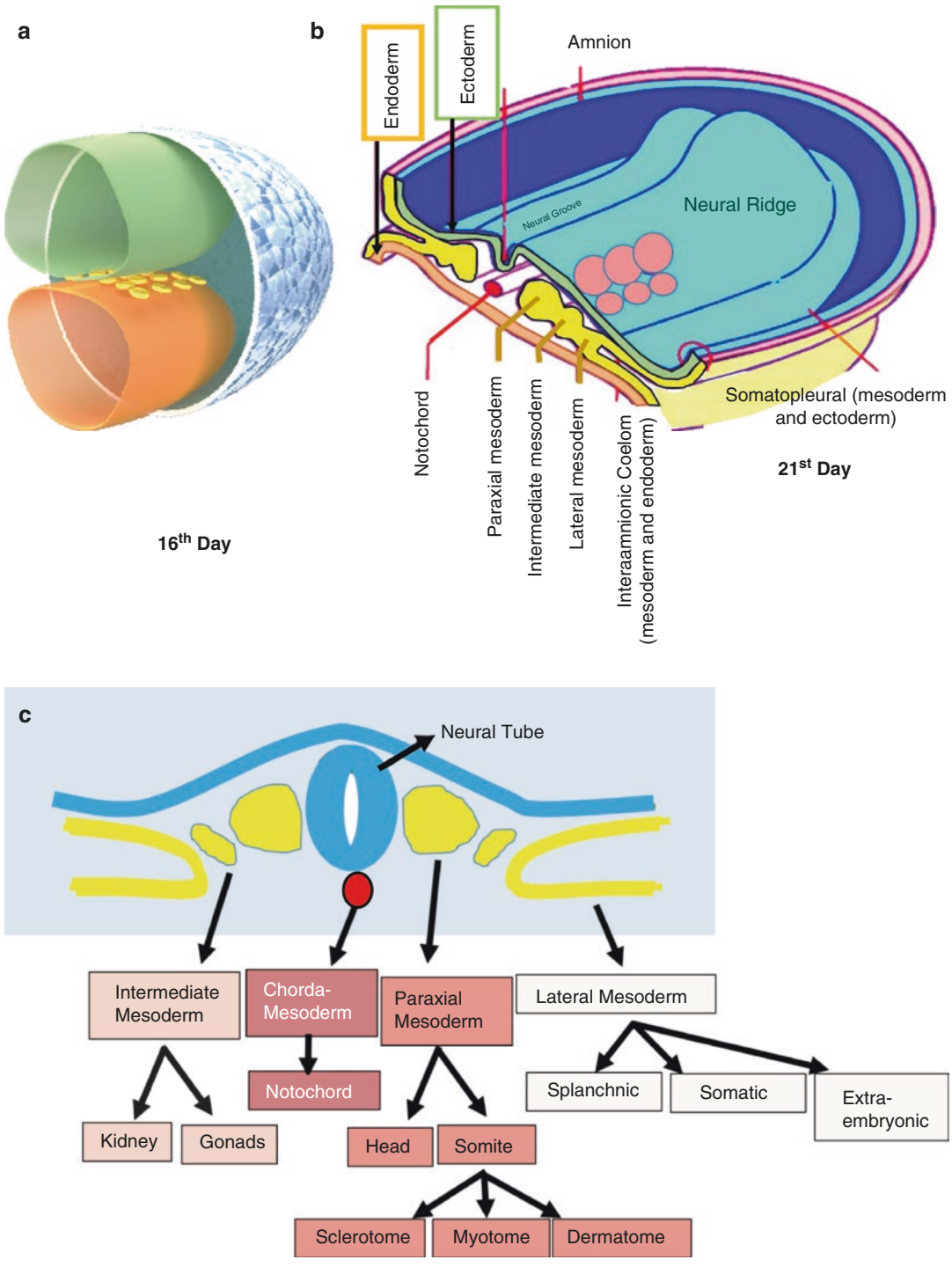

Fig. 2.6 Illustration of the embryonic development in the 21st day (first supporting structure (notochord) of the embryo)