10. DISCUSSION

Ilizarov methodology has been accepted as one of the modalities in treating open fractures, infective non unions, lengthening procedures, deformity corrections and in osteoporotic fractures. It is possible because of the structure of the apparatus which gives stability and rigidity. Stability is the ability of the fixator to maintain the necessary mechanical configuration during treatment: rigidity is a measure of the mechanical response of the fixator, which has importance in the healing response. The non linear behavior of the Ilizarov frame is attributable to increasing wire tension under loading. The Ilizarov frame is less stiff in bending, particularly in the lateral-medial direction, but its values for lateral-medial and antero-posterior bending are similar: bending stiffness increases with increasing axial loading. In torsion, the Ilizarov frames are somewhat less stiff [30].

The unique wire-ring combinations in the Ilizarov apparatus produces a much lower axial stiffness and axial loading force, which distributes load to all parts of the frame, than do the uniplanar fixators that use much heavier pins. At the same time it shows higher axial stiffness against loading from bending forces [21].

The most important factor governing rigidity of this frame is bone contact. The most flexible system (two 1.8 diameter smooth wires in each fracture component loaded to 110 kg in tension without bone contact) is only 6.1% as stiff in axial loading as the intact tibia without bone contact [31].cortical contact and compression- 1.8 mm wire with 110 kg tension, stiffness increases to 94.4% of intact. With eight wires and no bone contact, axial stiffness increases to 53.7 % of intact. While bone contact is the most important factor in gaining the axial stiffness, the number of wires governs the torsional stiffness of the frame [31].

Ilizarov external fixator could be viewed as a rigid beam whose sideways deflection was resisted by one or more resilient elements. The amount of displacement of a bone fragment under the influence of a loading force directly depends upon the fragments stability, which is determined by the stiffness of the wires and their placement with respect to the fragment and frame.

According to Pauwel's Theory and Ilizarov's Tension Stress Theory the cells can be regenerated using various biomechanical factors. For any tissue healing and regeneration vascular supply and stability are required. By giving stability to a structure the vascular supply is reestablished which is controlled by the genetic factors [51]. Even though there is a genetic inheritance to maintain the normalcy of the bone, the chemical mediator like growth factors [3, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, and 62] actually enables the process in day today activity. They influence cellular proliferation, chemotaxis and protein synthesis. The growth factors seem to play many critical roles in fracture healing, which involve a complex interaction of many local and systemic regulatory factors. Nearly all of the known mediators are derived from multiple locations and have multiple functions. These local mediators, along with the microenvironment, also influence gene coding for the type of matrix that the repair cells form.

Growth factors may be described as tissue-specific polypeptide that acts as local regulators of cellular activity. Growth factors exert their biologic function by binding exclusively to large, cell-surface transmembrane receptors on the target cell. On binding to the extra cellular domain of the transmembrane receptor, the intracellular domain is stimulated, leading usually to the activation of a specific protein kinase. The in vivo effects of the protein kinase cascade culminate in the activation of transcription of a gene into mRNA, which is then translated into proteins for use intracellularly or extracellularly [63].

Bone matrix contains numerous growth factors, including bone morphogenetic proteins (BMPs), transforming growth factor-beta (TGF-beta), insulin-like growth factors I and I (IGF-I and IGF-II), platelet-derived growth factor (PDGF), and acidic and basic fibroblast growth factor (aFGF and bFGF). Various osteoblastic culture models as well as in vivo experimental and clinical models have revealed that these growth factors influence cellular proliferation, differentiation, chemotaxis, and protein synthesis [53, 54, 56, and 57].

Fracture healing is an intricate biologic process in which structural integrity is restored through the regeneration of bone. Endochondral ossification, the process by which bone is formed from a cartilaginous precursor, and intramembranous

ossification, the process by which bone forms under a mesenchymal model, are subject to this distinct process that requires neoangiogenesis, recruitment of undifferentiated mesenchymal cells to the fracture site, and induction of these cells into osteoblasts and chondroblasts to generate new bone. Union, as an end point of regained structural strength, can be predicted confidently when bending stiffness reaches 7Nm per degree, and can be said to have been reached when stiffness reached 15 Nm per degree.

Delayed union is a process of union occurring by late intramedullary callus, the periosteal response having ceased before union was achieved. As an end point, delayed union is represented by evident cessation of periosteal new bone formation before union has been achieved, likely to be reflected by a bending stiffness less than 7Nm per degree by 20 weeks.

Non-union is a process of scar formation in which the rate of endosteal and periosteal osteogenesis is zero or low, being out weighed by bone resorption. As an end point, non-union, evidenced by cessation of periosteal and endosteal new bone formation, with sclerosis of the medullary canal observed at the fracture surfaces. If a phase of periosteal new bone formation take place, but without successful bridging, the morphology of the fracture ends will be hypertrophic, and the scar may be stiff. If no such phase ever took place, the morphology will be that of an atrophic nonunion with an elongated fracture gap and greater laxity [64]. This bone is then remodeled along the lines of stress according to the laws of Wolff.

In the absence of above-mentioned growth factors modern tissue engineering [65, 66,] tries to introduce osteoprogenitor cells, which can be osteoinductive under appropriate stimuli. Even after the synthetic replaced material is available at the site, any bone healing response requires vascularity and stability. The vascular bed acts as a vehicle to deliver inflammatory cells, which secretes stimulating factors. Vascularity also transports oxygen and nutrients to the repair site and acts as a conductive pathway for the endothelial cells and osteoblastic progenitors. The vascularity is improved by active loading of the limb, pretensioned wires and by distraction [67].

Kroese, studying the blood flow in tibiae, found that the rate was 4.1±0.8 ml/min in the resting state, but rose to 26.5±3.4 ml/min under the influence of functional loading – a six-fold increase [68].

In another experimental study on Distraction Osteogenesis in Dogs, Aronson J found at the distraction site, the flow increased to nearly ten times control, peaked at two weeks post operatively, and then decreased to four to five times the control for the remainder of the distraction time. During the consolidation period, significantly increased flow persisted at levels of two to three times control. The distal tibiae, away from the distraction gap, showed similar amplitude and temporal patterns of increase blood flow. No significant differences were found between the groups tested or when compared with similar fracture models [69].

The electrical effects of bone are broadly divided into the findings of dry bone piezo-electrical and those of wet bone in vivo streaming potentials. Yasuda reported that when hydrated long bones were loaded, the concave portion was negatively polarized and the convex part was positively polarized. In bones, the generation of voltage by stress is mainly associated with the existence of pseudo – crystalline collagen. These findings lead to the demonstration of piezo-electrical phenomenon in bone. (Fukada and Yasuda) [70].

Differential movement of ions within a structure leads to a short -lived change differential that behaves like a streaming potential. Neutrality is restored following equalization of ion distribution. The external distribution of the electrical potential difference, observed between the two outer surfaces, is much smaller than that observed locally in the walls of the osteons. This has been attributed to the streaming potential. (Polloch et al) [71].

Basset confirmed their earlier findings and later demonstrated bone formation at the negative pole and bone resorption at the positive pole with an applied current in vivo. Bone formed around normal electrodes without any potential difference. Insertion of a metal with in a bone is sufficient per se to stimulate bone deposition. Many investigators have shown that low level electrical currents can greatly influence cell activation and bone growth. Basset hypothesized that a primary step in translating

functional load bearing to an adoptive cellular response was linked to the electrical potential generated by the mechanical deformation of the bone tissue [71].

The mechanical environment like micromotion is an important biologic stimulus [72].

Yamagishi and Yashimura considered it helpful to preserve slight longitudinal mobility of the junction between the fragments, which allowed moderate repeated muscular pressure on the fragment ends [73].

Suitable dynamic axial stimulation can enhance maturation of distraction callus when the initial amplitude is small, but a large axial interfragmentary movement can lead to delayed union [74].

The musculoskeletal system undergoes constant micro movement in response to mechanical influences. Micro movements are thought to have an important influence on the healing of the fractures, development of arthritis and osteoporosis, and the body's response to prosthetic implants. At one magnitude, micro movement has shown to promote the healing of fractures, but at a higher magnitude it inhibits healing [75].

A cascade of biologic processes that may include differentiation of pluripotential tissue, endochondral ossification and bone remodeling accompanies skeletal regeneration. It has been shown that all these processes are influenced strongly by the local tissue loading history. Cyclic motion and the associated shear stresses cause cell proliferation of large callus in the early phases of fracture healing. Increasing movement stimulated callus formation but not tissue quality. For intermittently imposed loading in the regenerating tissue (1) direct intramembranous bone formation is permitted in areas of low stress and stain; smaller than approximately 5% and small hydrostatic pressure (<0- 15 MPa). Proliferation and transforming growth factor beta production was increased for strains up to 5%, but decreased for higher strains. (2) Low to moderate magnitudes of tensile strain and hydrostatic tensile strain may stimulate intramembranous ossification. (3) Poor vascularity can promote chondrogenesis in an otherwise osteogenic environment; (4) hydrostatic compressive stress is a stimulus for chondrogenesis. Strain less than 15%

and hydrostatic pressure more than 0.15MPa stimulated endochondral ossification. (5) High tensile strain is a stimulus for the net production of fibrous tissue and (6) tensile strain with a super imposed hydrostatic stress will stimulate the development of fibro cartilage.

Finite element models are used to show that the patterns of tissue differentiation observed in fracture healing and distraction osteogenesis had been predicted from these mechanobiologic concepts. In areas of cartilage formation, subsequent endochondral ossification normally will proceed, but it can be inhibited by intermittent hydrostatic compressive stress and accelerated by octahedral shear stress (or strain). Late bone remodeling at these sites can be expected to follow the same mechanobiologic adaptation rules as normal bone [76].

Gurlt [43] – mutual compression of fragments stimulates osteogenesis. Surgeons have long known that wound surfaces need mutual contact to heal rapidly. The bone tissue also responds in the same way. Only precise and complete repositioning of fresh fragments will promote rapid osteosynthesis. Complete reduction and close contact of congruent fragment ends provide a large contact area- the conditions needed for firm “primary adhesion”. In this situation, direct consolidation of a fracture begins at the initial stage of fracture healing; a minimal amount of callus is required. Syngaevsky, [45] found direct consolidation when no mutual fragment was present. If no cartilage formed, healing was nine times faster than in areas where a cartilaginous phase was created by mutual fragment motion. When motion is present at fracture surface, bone resorption always occurs and healing takes place via a primary fibrocartilaginous stage and slower the consolidation. The reparative reaction depends on arterial hypervascularisation. When the fragment ends are mobile, the moving bone ends traumatize the local blood supply. Compression osteosynthesis with a constant pressure on bone tissue of up to 150KPa does not suppress the reparative process and does not cause damage or resorption of the bone tissues. It is evident that osteogenesis depends significantly upon the state of blood supply and influence of axial compression and other forms of mechanical loading [67].

Gradual traction on living tissues creates stresses that can stimulate and maintain the regeneration of active growth of certain tissues. Slow, steady traction of tissues causes them to become metabolically activated, resulting in an increase in the proliferative and biosynthetic functions. These processes are dependant upon the adequacy of blood supply to the tissues being elongated and the stimulating effect of weight bearing and functional use [27].

This method was developed and refined by Ilizarov, using external fixators and small diameter wires (1.8mm) under tension – 50-130 kg/sq.cm. [14] Elongation by 1 mm per day in four equal increments - 0.25 mm every 6 hours, led to more favorable results. When the auto distracter was used 1mm in 60 steps, 0.0085 mm every 24 minutes for limb lengthening, the proliferative, metabolic and biosynthetic changes in cellular activity in many tissue elements took on features characteristic of histogenesis during embryonic fetal and post natal growth. The new bone can form in any plane and distraction osteogenesis always follows the vector of applied force. The latency period of 5 to 7 days is required. The initial latency period appears to be no different than routine fracture healing.

The quality of the new bone formed depends on number of factors.

1) The rigidity of bone fragment fixation,
2) The degree of damage to the marrow, the periosteal soft tissues, nutrient artery and its branches,
3) The rate of distraction.
4) The frequency of distraction [27].

The hypotheses and current research have furthered knowledge of the molecular mechanisms that govern distraction osteogenesis. Recent studies have implicated a growing number of cytokines that are intimately involved in the regulation of bone synthesis and turnover. The gene regulations of numerous cytokines (transforming growth factor-beta1, -beta2, -beta3), bone morphogenetic proteins, insulin-like growth factor-1, fibroblast growth factor, and extra cellular matrix proteins (osteonectin, osteopontin) during distraction osteogenesis have been best characterized. It is believed that understanding the biomolecular mechanisms that mediate membranous distraction osteogenesis may guide the development of targeted

strategies designed to improve distraction osteogenesis and accelerate bone healing (37).

Another study performed to investigate the effect of loading on the biology of newly forming bone during limb lengthening, in situ hybridization for osteocalcin and collagen I, and antibody staining for collagen II and BMP 2,4 were used to evaluate the molecular influence of loading. There was more new bone in the distraction gap of the weight-bearing animals than there was in the non-weight-bearing animals. BMP 2/4 expression, and the messages for collagen I, and osteocalcin, were more abundant in tissue from the weight-bearing animals; collagen II was higher in the non-weight-bearing animals. This suggests that early regenerate tissue is capable of responding to loading, and that weight bearing appears to stimulate intramembranous ossification. These findings support the concept of early weight bearing after limb lengthening (38).

In one another study to determine the effect of continuous cyclic mechanical stretch as a fundamental event in distraction osteogenesis on the expression of 3 bone growth factors, transforming growth factor-beta 1(TGF-beta -1), insulin-like growth factor 1 (IGF-1), basic fibroblast growth factor (bFGF) and 2 cytokines, interleukin (IL)-1 (IL-1) and 6 (IL-6) in human osteoblast-like cells.

After 8 hours, mRNA for TGF-beta 1 and IGF-1 increased in the experimental group, whereas bFGF decreased but cytokines IL-1 and IL-6 were not affected. At 16 hours, TGF-beta 1, IGF-1, and bFGF showed increased levels of mRNA; IL-6 showed a slight increase. After 24 hours, TGF-beta 1, IGF-1, bFGF, and IL-6 had increased mRNA levels. IL-1beta did never show significant alterations in mRNA production as compared with the control.

Tensile stretch on osteoblast-like cells alters local regulation of bone formation, increasing the expression of bone growth factors; where as catabolic cytokines are unaffected. These findings suggest a direct effect of mechanical strain on osteoblasts and may be the driving factors of bone growth during distraction [39].

Pluripotential gap tissues are sensitive to their physical surroundings. Mechanisms responsible for this include vascularity, stem cell supply and scaffolding

architecture. 3 types of ossification is seen the zone of regenerate. James Aronson [40] noticed intramembranous ossification could be irregular and islands of endochondral ossification. According to Richards et al, [41] both endochondral and intramembranous bone formation were observed through out the consolidation period. Yasui et al [42] observed 3 types of ossification. Typical endochondral ossification was prominent in the early stage of distraction, but intramembranous bone formation became prominent mechanism of ossification at later stages. They demonstrated a third mechanism of ossification 'transchondroid bone formation'. Chondroid bone, a tissue intermediate between bone and cartilage, was formed directly by chondrocyte like cells, with transition from fibrous tissue to bone occurring gradually and consecutively with out capillary invasion. In situ hybridization using digoxigenin- 11-UTP- labeled complimentary RNAs showed that the chondroid bone cells temporarily expressed type II collagen mRNA. They did not show the classical morphological characteristics of chondrocytes, but were assumed to be young chondrocytes undergoing further differentiation into bone forming cells.

Recently, there are number of articles are coming on growth factors and it is relation to mechanical factors on bone healing and regeneration. When they are completely understood can be utilized, as the situation is required.

The functional loading of the limb is possible only when the mechanical stability is there. Biomechanically the Ilizarov Ring Fixator System has got the versatility to apply for any orthopedic condition and provides the desired stability in a segmental defect, shattered fractures and in osteoporotic bones. This character of the ring is studied in our clinical materials and has given 97.3% success in different difficult situations, with less number of secondary procedures, complication and a shorter healing time. In Shved et al series 85% out of 36 patients had functional recovery [46]. In another study by Shaved et al, they claim the disability is reduced by 3-4 times when ring fixator is used and 95.3% had functional recovery [47]. According to Kallayev study on juxta and intra articular fractures out of 149 patients treated by ring fixator, all of them retuned to their original job [48]. In a study by Okulov out of 49 intra articular fractures all of them regained functionally useful range of movement and weight bearing [49]. Okhotsky et al in their study of ring fixators in open fractures, out of 124 cases healing occurred in 93.3 % of the cases

and the risk of development of osteomyelitis was reduced from 22% to 6% [50]. Makushin proposed the ‘APPARATUS LIMB’ concept because the frame was able to support the limb in major gaps and during distraction osteogenesis. Further going in to find out how it is working Our Finite Element study has shown that all the stress goes through the ‘K’ wire which are already pretensioned attaching at both the ends of the ring and in the displacement study the four ring construct gives the best stability with the possibility of micromotion.

The results of the finite element study with above diagrams shows the whole stress goes in the wires in transverse fracture stabilization with a fracture gap of 1 mm. The displacement graph shows there is least displacement of 0.1 mm in 4-ring construct with pretensioned wires and there is 0.5 mm displacement in 2-ring construct with wire pre tension and 0.7 mm displacement in 2 ring construct with no wire pretension. This study shows Ilizarov ring fixator system is biomechanically stable, yet dynamic with tensioned thin wires.

Along with the above finding, the mathematical model of ossification shows best bone regenerate is possible in the four ring construct where closed osteotomy was done, which proves more than mechanical stability biological factors are also involved in bone healing and regeneration. The mechanism of the bone formation has followed the first order kinetics.

For bone healing and regeneration stability and vascularity are required. Biomechanically the ring is stable in static and dynamic loading allowing for cyclical axial loading both in fracture healing and distraction osteogenesis. Our basic model finite element analysis shows in various constructs all the stresses are taken by the wires.