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Morphological Prenatal Studies on Some Structures of the Developing Human Knee Joint, Part 3-Some Morph- Histological Studies on the Prenatal Developing Synovial membrane, (stratum synoviale), the ligamentum Patellæ (anterior ligament) and Patella of the human Knee Joint. (Articulatio Genu)

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Abstract: The synovial membrane was announced as forgotten tissue by some investigators. Recently the involvement of the human knee joint synovial membrane in knee diseases was proved. The present work studies some histological changes of the synovial membrane (SM), the ligamentum Patellæ (LP), and the Patella (P) of the prenatal developing human knee joint. The work produces new data about the morpho-histological changes of the (SM), (LP), and P with age progress of the developing prenatal human knee. Thirty-three human male and female fetuses aged (4) months (13-16wks-CRL 9-14cm), full term 9 months (33-36 weeks-CRL 31-34cm) and newborn infant (37-38 weeks) CRL 35-36cm), besides four adult male and female knees for comparison were used. The fetuses were collected from the miscarriage and spontaneous abortion, with no lacerations or abnormalities obtained from Gynecology and Obstetrics Department Al -Zharaa hospital-Cairo -Egypt (according to medical ethics). Specimens from the synovial membrane SM of 4 months fetuses and full term. Ligamentum Patellæ LP, and the patella P of full term were collected freshly and fixed in formalin. for 10 days, then dehydrated, cleared in benzene, embedded in paraffin wax, cut serially at 7 microns thickness and stained with haematoxylin and eosin, Mallory's triple stain, Masson trichrome stain to investigate collagenous tissue, Van Gieson to illustrate collagen and elastic fibers and also Mallory's triple stain, besides silver impregnation –Gordon and Sweet to illustrate neuroreceptors and free nerve endings. Histological study by light microscope of sections of parts of the synovial membrane (SM) of 4months fetus showed that it was formed of intima, subintima and deep synovium, intimal velli were noted. The intima was formed of3-5 layers of pleomorphic synoviocytes (Type A: Macrophage like synoviocytes (MLS) and (Type B: Fibroblast like synoviocyes FLS). The subintima contained areolar adipose tissue, fibroblasts, macrophages, loosely packed collagen bundles, elastic fibers, few lymphocytes, blood vessels and capillaries. The deep synovium contained short collagen bundles, elastic fibers, blood vessels and many capillaries. The synovial tissue of full term was formed of intima, subintima and deep synovium. The intima formed of 1-2 layers of pleomorphic synoviocytes. The velli increased in length and depth than the previous age. The sub intimal collagen bundles were densely packed increased in length and thickness. Some collagen bundles had special arrangement in deep synovium. Macrophages, elastic fibers and fibroblasts, and, (mature &none mature) blood vessels and many fenestrated capillaries increased in synovial tissue with age progress more than the previous age. In the sub intima of full-term fetus, giant cells with podia and ruffled cytoplasm secreting collagen were noted. Few Undifferentiated mesenchymal cells UMCs were detected. Histological examination of sections stained by Mallory triple stain of parts of the the deep subintimal synovium of 4month fetus (13-16wks-CRL 9-14cm), showed the presence of free nerve endings around the blood vessels, Small Pacini-like corpuscle, Raffini-like nerve endings structures with button ends. Histological examination of sections stained by Gordon and sweet-silver impregnation method, of parts of the synovial membrane (SM) of full-term fetus of the human knee joint, showed the presence of mechanic neuro structures, similar to Raffini endings with button ends, Meisseners like-corpuscles with zigzag or spiral nerve ending cours inside the capsule giving the corpuscle a striate appearance. Sometimes two corpuscles shared one branched axon. Pacini like-corpuscles were in clusters around blood vessels, elongated large single Golgi tendon stretch –like organ with peri-axial space and capsule enclosing large component and sensory terminal were noted. Free nerve endings FNE were seen. Meissener's corpuscle like structures in the synovial membrane (SM) of full term fetus of the prenatal developing human knee joint was not reported in the literature. The presence of mechano neuro structures in the synovial membrane (SM) of full term fetus of the prenatal developing human knee joint indicated sensory function of the synovial membrane (SM). Histological examination of

serial sections of part of the ligamentum patelle (LP)of full term (33-36 weeks) CRL 31-34cm) stained by Van Gieson stain showed long thin collagen bundles interlacing regularly in parallel DIFFERENT directions. Masson trichrome stain showed that the collagen was interlacing with elastic fibers which had curved ends, arranged parallel regularly. Ligamentum patellea (LP) had fibers oriented in a range of directions to resist bone separation in more than one direction. Histological examination of serial sections of part of the growing patella (P) stained by Van Gieson stain of the full-term human:(33-36 weeks) CRL 31-34cm) showed the presence of two differently stained areas: lightly stained stratum, showing interstitial growth from inside in the cartilage, and darkly stained stratum, showing the appositional growth from outside occurred in the CT perichondrium. Conclusion: the histological changes in the synovial membrane of the prenatal developing human knee joint with age progress were noted in the form of increased collagen density, length, thickness and types with age progress. Some collagen bundle had special arrangement in the deep synovium of full term. Increased macrophages, fibroblasts, elastic fibers, and increased mature blood vessels with age progress occurred. Decreased intimal layers and increased velli length with age progress were noted. Few lymphocytes in the subintima probably for homeostasis and traffic function of the synovial membrane were noted. The changes in the Synovial membrane (SM) with age progress were essential for Synovial membrane function, immunity and other properties of the developing prenatal human knee joint. Histological examination of ligamentum patelle (LP) of full term showed special arrangement of collagen in different direction to restrict bone separation. The presence of interlacing elastic fibres and collagen in the prenatal developing (LP) of the human knee joint was to allow range of movements. The Changes in the growing patella (P) in the hyaline cartilage interstitial growth and CT perichondrium appositional growth were noted to accommodate the knee functions and kinematics. Histological examination of sections stained by silver impregnation Gordon and Sweet, of parts of T S of the subintima of synovial membrane SMof full term fetus of the developing prenatal human knee joint, showed the presence of structures resembled Messienrs corpuscle, one branched axon supplied two Messienrs like Corpuscles; one corpuscle had zigzaz appearance and the other had spiral or striate appearance. Raffini like Corpuscles had ramifications and button endings, Pacinian like corpuscles were present in clusters near the blood vessel. Pacinian like corpuscles had arranged cells in lamellae around a core. One axon was attached to three Pacini corpuscles. Structure similar to Golgi tendon organ was present single, elongated, oval, not near blood vessels, with large components and sensory terminals inside a capsule, and a peri axial space around the capsule. Golgi tendon like organs were noted less than Ruffini like sensory endings. Golgi like tendon organ had the largest volume among the four types of the neuroreceptors found in the synovial membrane of the prenatal developing human knee joint in the present study. Free nerve endings FNE near blood vessels were observed. Pacinian corpuscles seemed to function in group mode when stimulated momentarily as they were found in groups. The presence of these structures that resembled the mechanoneurorecptors in the synovial membrane of the 4month fetus and full term of the developing prenatal human knee joint indicated sensory functions of the prenatal human synovial membrane. Raffini mechanoreceptors were thought to contribute to muscle tone maintenance, Golgi tendon stretch like organs and Pacinian corpuscles were stimulated during knee joint movement, and the free nerve endings were nociceptors, involved in pain transmission and modulation of pain transmission. Thus, receptors of the prenatal developing synovial membrane of human knee joint were able to produce a discriminating afferent inflow to the central nervous system (CNS), there by contributing to the biomechanics, kinematic, protection, pain transmission and modulation of pain of the prenatal developing human knee joint through the musculature. In the present study, fortification of the knee by the synovial membrane, patella and ligamentum patellae, besides another knee joint ligaments and structures like collateral, cruciate, meniscofeoral ligaments and menisci. Coincided with Suret al ensan 28 in the Holy Quraan. The presence of different types of cells, and various neuro receptors, nerve endings NE, besides different TYPES OF collagens, noted by histological examination by light microscope in the synovial membrane SM of the prenatal developing human knee joint. - which was called the forgotten tissue -indicated the presence of powerful Creator Allah the most merciful the most graceful. Surety al threat 21. fuselat53.

[Manal G. Abdiwahab; Sohair A. Sadek; Marzouk, Sarah M **Morphological Prenatal Studies on Some Structures of the Developing Human Knee Joint, Part 3-Some Morph- Histological Studies on the Prenatal Developing Synovial membrane, (stratum synoviale), the ligamentum Patellæ (anterior ligament) and Patella of the human Knee Joint. (Articulatio Genu)** *J Am Sci* 2023;19(5):1-40]. ISSN 1545-1003 (print); ISSN 2375-7264 (online). http://www.jofamericanscience.org 01.doi:10.7537/marsjas190523.01.

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Introduction

Henry Gray (1821–1865) mentioned that the Knee-joint (Articulatio Genu) was a ginglymus or hinge-joint, but was really of a much more complicated character. It had to be regarded as consisting of three articulations in one: two condyloid joints, one between

each condyle of the femur and the corresponding meniscus and condyle of the tibia; and a third between the patella and the femur, partly arthrodial, but not completely so, since the articular surfaces were not mutually adapted to each other, so that the movement was not a simple gliding one. That view of the construction of the knee-joint received confirmation from the study of the articulation in some of the lower mammals, where, corresponding to these three subdivisions, three synovial cavities were sometimes found, either entirely distinct or only connected together by small communications. That view was further rendered probable by the existence in the middle of the joint of the two cruciate ligaments, which had to be regarded as the collateral ligaments of the medial and lateral joints. The existence of the patellar fold of synovial membrane would further indicate a tendency to separation of the synovial cavity into two minor sacs, one corresponding to the lateral and the other to the medial joint

Gardner & Gray (1953) mentioned that the intermediate stratum merged with the general mesenchyme of the limb, which was vascularized. From that, a cuff condensed as the fibrous capsule of the joint, in continuity with the perichondrium of the bones concerned. A thinner layer of vascular mesenchyme was enclosed within that as the precursor of the synovial capsule (Haine, 1947; Gardner & Gray, 1950; Gardner & O'Rahilly 1968).

O'Rahilly (1954) studied the prenatal development of the human centrale and O'Rahilly and, Gardner (1975) established the timing and sequence of events in the development of the limbs in the human embryo.

Castor (1962) pointed that human synoviocytes were generally elliptical, with numerous cytoplasmic processes but could vary considerably in form. They consisted of at least two morphologically distinct populations, termed type A and type B synoviocytes.

El Rakawy (1971) mentioned that fibroblasts were the commonest, the most important branched cells in the connective C.T tissue proper. They had large pale nuclei with fine chromatin granules. Their cytoplasm did not contain particles. Fibroblasts formed all types of C.T fibers. Macrophages were the second common highly phagocytes, fixed and could become free and move, and could be demonstrated by intravital staining. They had dark nuclei with coarse chromatin granules. Their cytoplasm was full of particles which they phagocytized.

Williams & Warwick (1992) pronounced that the functions of the cells of the synovial intima included the removal of debris from the joint cavity (mainly by type a cells and the synthesis of some of the components of the synovial fluid (by both types of cells).

Bellelli et al. (1996) studied the Synovial cyst of the cruciate ligament with magnetic resonance in 8 symptomatic cases;and mentioned that the intra-articular cyst were uncommon finding : only 30 cases had been reported since the first paper by Caan in 1924, and they were all associated with cruciate ligaments.Many different cystic or pseudocystic lesions were found in articular knee joint conditions;the most common cystic lesions were popliteal cysts (Baker, s cysts),followed by Synovial pseudocyst of the posterior cruciate ligament, meniscal cysts.and finaly ganglionic cyst of the anterior cruciate ligaments.They added that the origin of the ganglionic cysts in the cruciate ligaments was still unknown,even though many theories had been suggested, including a synovial herniation in the ligament fibers, the ectopic inclusion of synovial tissue,a post traumatic connectival degeneration and, finally the proliferation of totipotent mesenchymal cells.They pointed that,from histological point of view,"synovial ganglion" was much better definition than "synovial ganglion cyst ", because the typical wall of the real synovial cyst was missing .The MR patterns were typical of the morphological features described and the presence of high protein fluid content .

Mérida-Velasco et al. (1997) summarized their observations of the development of the knee joint in 50 serially sectioned human embryonic and fetal lower limbs (26 embryos and 24 fetuses). They established the morphogenetic time table of the human knee joint and announced that epiphysis of the femur and tibia became condryfied from O'Rahilly stage 18, and ossification began during the 13th week of development. The patella appeared as a dense blastema during O'Rahilly stage 19, became condryfied during O'Rahilly stage 22, and began its ossification during the 14th week of development. The knee joint cavity appeared during O'Rahilly stage 22, initially as the femoropatellar joint.That process began at the periphery of the articular interzone. The superior tibiofibularjoint communicated with the lateral meniscotibial joint between 10 and 11 weeks of development and became separated from the13 week on. The menisci arose from the eccentric portions of the articular interzone during O'Rahilly stage 22; however, until week 9 of development, they were not easily distinguishable.

Ratajczak (2000) investigated 43 serially sectioned human embryos of developmental stages 18 to 23. They observed the homogeneous interzone of the future knee joint in embryos at stage 18. They mentioned that during stage 19 that interzone was differentiated into dense, intensively stained, peripheral parts, which were the primordia of menisci and the medial portion, in which the cruciate ligaments were formed. All structures of the interior of the knee joint

were more clearly delineated during stage 20, and they were well developed during the last embryonic week.

Rafael Iñigo Pavlovich (2008) reported that the normal synovial membrane had a variable architecture, including thickness of the lining and the subintimal cell infiltrate, with little inflammatory cytokine production or expression of cell adhesion molecules. The excess of osteoprotegerin expression over receptor activator of nuclear factor kappa ligand and IL-1 receptor agonist over IL-1 might be important for protection against joint damage. Interleukin-1 receptor antagonist was frequently detected in the synovial membrane of normal patients, but both tumor necrosis factor alpha and IL-1b were rarely detected. In addition, cell adhesion molecules were rarely detected in the normal synovial membrane, with the exception of intercellular cell adhesion molecule-1 and vascular cell adhesion molecule-1. Osteoprotegerin expression was abundant in parasynovial macrophages as well as endothelial cells, but receptor activator of nuclear factor kappa ligand expression was rarely seen. They added that in nonrheumatic pathological conditions, the synovial irritation might result from mechanical injury, either traumatic or as a result of repetitive microtrauma, or as a result of altered metabolism, the latter was usually associated with chondral pathology. A vicious cycle might begin with an injury of the cartilage by overload or repetitive microtrauma. When chondral fragments were sensed by the synovium, synovial cells might respond by release of cytokines creating inflammation. If that persisted, synovial fluid would no longer properly nourish health cartilage leading to continued degeneration and accelerated cytokine release.

Freeman and Wyke (1967) classified encapsulated nerve endings in the synovium of the cat joints after anatomical and histological study as follows: Ruffini endings were(Type 1), mechanoreceptors ,slow adapting, low threshold, Pacinian corpuscles were(Type 2), rapidly adapting, low threshold mechanoreceptors; Golgi organs(Type 3), characterized by their poor association with blood vessels were slowly adapting, high threshold, mechanoreceptors; and free nerve endings were pain receptors (Type 4). Another worker; Grönblad et al., pointed that substance P-immunofluorescent nerves were associated with pain transmission and were found in human knee synovial membrane and menisci. Both tissues also contained enkephalin-immunofluorescent nerves, which might be participated in pain modulation transmission. Thus Immunohistochemical methods confirmed the presence of nociceptive receptors in those joint structures that were found previously on histological basis.

Smith (2011) mentioned that the synovial joints were involved in a number of immunological and inflammatory disorders, including RA, systemic lupus erythrematosis and spondyloartheritis. Undestanding the microstructure of the normal synovium, including the wide range of microscopic appearance, cellular infiltrates and production of cytokines, enzymes, including biologically relevant proteins ,would assist in understanding the changes in synovial tissue architecture and immunopathology in diseases. While the architecture of normal synovium was not as homogenous as previously thought in rheumatology texbooks,there were consistencies across the broad spectrum of normal synovial tissues which could be contrasted with what seen in the chronically inflamed synovial tissue .The marked increase in synovial layer thickness, with reverse in normal ratio of Type A to type B synoviocytes,favouring type B cells in normal synovium and type A in RA, was an example of that numerous other examples could be given including the changes in subintimal cell content, cytockines and chemokine production,vascular and lymphatic changes as well as production of metalloproteinnases and stimulators of osteoclast formation.It was important to understand the chronology of those synovial changes in chronic inflammatory arthritides and contrast them with that seen in normal synovium. The identification of TNF-a and IL-IB as two likely therapeutic targets were examples of how such a strategy could lead to useful therapeutic interventions in management of several chronic inflammatory arthritis including RA, psoriatic arthritis and ankyosing spondylitis .There was still much to be learned about the immunological microenvironment of the articular tissue, particularly the normal synovium.

Fidel Hita-Contreras et al. (2012) observed the synovial membrane in week 13in the prenatal developing human wrist joint in their study of the development and morphogenesis of human wrist joint during embryonic and early fetal period. They mentioned that, the interzonal mesenchyme of developing synovial joints became trilaminar as a more tenuous intermediate zone appeared; splitting the mesenchyme into two dense strata next to the cartilaginous ends of the skeletal elements of the region. As the dense strata of the interzonal mesenchyme also became cartilaginous, subsequent cavitation of the intermediate zone established the cavity of the joint. The loose vascularized mesenchyme around the cavity formed the synovial membrane (stratum synoviale) and probably also gave rise to all other intra-articular structures (Gardner, 1963; Genis, 1970; Moore & Persaud, 2000; Moore et al. 2008; Standring, 2008).

Some workers referred that the origin of the fibrous capsule (stratum fibrosum) of some synovial joints was the interzonal mesenchyme (Gardner, 1963; Gardner & O'Rahilly, 1968), whereas other

researchers ` supported an extramesenchymal origin (Haines, 1947).

The synovial membrane (also known as the synovial stratum, synovium or stratum synoviale) was a specialized connective tissue that lined the inner surface of synovial joints,capsules and tendon sheaths.

Rafael Iñigo Pavlovich (2008) reported that the synovial membrane was termed the forgotten tissue The Synovial membrane was one of the most studied recently and analyzed structures in the human knee joint because it was involved in pain and knee joint problems as, osteoarteritis, OA, rheumatic arthritis RA ,and other diseases especially in the elderly (Yves Henrotin, et al., 2014, Korochina et al., 2016, Manferdini 2016 et al; Belluzzi et al ., 2019)

Yves Henrotin, et al. (2014) stated that in diarthrodial joints in adult, the synovial membrane intima consisted of a thin layer of cells with phenotypic characteristics of fibroblasts or macrophages. Those cells were a major source of synovial fluid components which were directly involved in maintaining the cartilage integrity by lubricating the cartilage surface and by modulating chondrocyte metabolism. Two important molecules produced by synovial lining cells hyaluronic acid and, lubricin, contributed to protect articular cartilage surfaces in diarthrodial joints (Rhee et al.2005), Ludwig et al. (2012) pointed that lubricin reduced pathological deposition of protein at the cartilage surface and protected articular surface. The SM provided essential nutrients for maintaining chondrocyte activity and participated in the removal of products of chondrocytes metabolism and articular matrix turnover. Normal SM acted also as a semipermeable membrane, controlling molecular traffic into and out of the joint space and maintaining the composition of synovial fluid. Beside 'fibroblastic-like' and 'macrophage-like' cells, the SM also contained mesenchymal stem cells with multipotency which was able to differentiate into multiple mature cell lineages including cartilage, bone, muscle or adipose tissue.

Schindler (2014) studied the morphology, embryology, pathophysiology and treatment of synovial plicae of the knee and the clinical and therapeutic aspects of the plica syndrome. They mentioned that a blunt trauma, a sudden increase in athletic activity or any form of transient synovitis were associated with plica inflammation leading to tissue fibrosis and subsequent loss of elasticity. They found that a plica affected in that way might impinge against intraarticular structures in its proximity, often creating localized chondromalacia particularly of the patellofemoral joint. The diagnosis was based on history and clinical examination although MRI could be of value. Twenty-three studies assessing the clinical outcome of 969 patients following open or arthroscopic plica excision were identified. The average age was 25 years with equal male-to-female ratio. They concluded that trauma was considered the cause in 57 % plica affection. At a mean follow-up of 27.5 months, 64 % of patients were symptom free, 26 % improved and 10 % considered failures. The author added that symptomatic plica might initially be treated with physiotherapeutic measures and structured exercise regimes but success rates were generally low. Intra-plical or intra-articular corticosteroid injections might be beneficial if administered early in the disease process.

Manferdini et al. (2016) reported that Synovial inflammation was a process characterized by synovial thickening (hypertrophy and hyperplasia) and cell infiltration (lymphocytes and macrophages). Histological analysis of synovium in OA showed an increased number of lining cells and infiltrating cells, mainly consisting of macrophages .with a very low percentage of B and T cells . Synovial inflammation was now accepted as an important feature of the symptoms and progression of OA.

Belluzzi et al. (2019) mentioned that the role of the synovial membrane was the production of the synovial fluid (SF) by cells from the synovial membrane intimal layer secreted the SF for the promotion of skeletal movement. The synovial fluid (SF) facilitated low-friction and low-wear articulation filling the synovial cavity, lubricating cartilage, and tendon surfaces, and sustained chondrocyte activity and nutrition. They pointed that inflammation of the Infrapatellar Fat Pad (IFP)and synovial membrane within the knee might have a central role in oasteoartheritis OA pain and might drive peripheral and central sensitization in Knee OA. They suggested that preventing sensitization to reduce persistent pain in KOA would be a potentially effective and novel means of preventing worsening of pain in knee OA ,since sensitization was associated with pain severity in KOA and might potentially contribute to the transition from acute to chronic,. Early targeting of inflammation in knee OA might therefore be a reasonable strategy to prevent the sensitization and thereby reduce pain severity. They concluded that OA was a complex painful, multifaced, and disabling disease. The only effective treatment for end-stage Knee OA patients was the total joint replacement. U nderstanding OA etiopathogenesis and pain mechanisms was a priority in order to identify new therapeutic targets to counteract and manage OA ,as pain and obesity incidence were rising also the prevalence of OA was expected to grow in the next years. There still need to understand more about individual symptoms and their relationship to particular structural pathologies. Importantly, pain was a complex experience in which changes might be attributed to several peripheral nociceptive factors other than inflammation, as well as central factors.

Sadler (2019) mentioned that the synovial joints between the bones began to be formed at the same time that the mesenchyme condensations initiated the process of forming cartilage ,Thus in the region between chondrifying bone primordial, called the interzone(e.g between the tibia and femur at the knee joint) the condensed mesenchyme differentiated into dense fibrous tissue ,That fibrous tissue then formed articular cartilage covering the ends of the two adjacent bones,the synovial membranes, and the menisci and ligaments within the joint capsule (e,g the anterior and posterior cruciate ligaments in the knee).The joint capsule itself was derived from mesenchyme cells surrounding the interzone region.Fibrous joints(i,e the sutures of the skull) also formed from the interzone regions interzone region remained as a dense fibrous suture .

Sadler (2019) stated that although patterning genes for the limb axes had been determined the limb that corresponded to the proximal (styloid dermined, it was HOXgenes that regulated the types and shapes of the bones of the limb. That HOX gene expression was depend on the combination expression of FGF, SHH, and WNTa genes that caused HOXgene expression in three phases in the limb that corresponded to the proximal (stylopod,humerous and femur)middle zeugopod: radius/ulna and fibula,and distal autopod: hand and foot) regions. genes of HOXA and D clusters were the primary determinants in the limb accounting for pattering the bones. Thus either mis-expression of those two genes might result in limb truncation and anterior – posterior duplications.Just as in craniocaudal axis embryo, HOXgenes were nested in overlapping pattern of expression that somehow regulated hind limb were the transcription factorsTBX5 (forelibm) and TBX4 together with PITX1/(hind limb).

Histopathological examination of synovial biopsy played a vital role in distinguishing between various possible etiologies such as infective, traumatic or crystal-induced arthropathy and neoplastic lesions. Clinical and radiological findings were also essential in arriving at an accurate diagnosis of synovial lesions. They aims to study the spectrum of synovial lesions and correlate clinicoradiological findings of various lesions into degenerative, infective, inflammatory and neoplastic lesions. Tht ollected the synovial biopsy specimens from the Pathology laboratory, KIMS Hospital and Research Centre. Detailed histopathological studies of the sections were done. Relevant clinical and radiological findings were analysed that found, the common age groups affected were between 2nd decade to 3rd decade (31.1%) and above 5th decade (31.1%). Females (56.6%) were more commonly affected. The knee joint (43.3%) showed a predilection for most synovial lesions. Among all the cases most common was tumour-like lesions (42.2%) followed by inflammatory lesions (19.9%), degenerative lesions (16.6%), infective lesions (9.9%), benign (9.9%) and malignant lesion (1.1%). They concluded that most synovial lesions had identical clinical findings classified into various subgroups by histopathological study. The study of synovial biopsy was a useful diagnostic tool in assessing various joint diseases.

Banios et al. (2022) reviewed mechanoreceptors in the Anterior and Posterior Cruciate Ligaments and reported that Schultz et al. were the first to demonstrate the histology of MRCs in human cruciate ligaments (using gold-chloride staining techniques), taken at the time of amputation or autopsy. They found 1–3 Golgi organs in each ligament, located at the surface of each ligament beneath the synovial membrane. Zimny et al. (1986) presented for the first-time a histological demonstration of two morphologically distinct MRCs in the human ACL, as they identified Ruffini and Pacinian corpuscles in 6 human subjects

Many studies of the synovial membrane and its role in knee diseases were done .However histological studies of the prenatal developing human synovial membrane (SM), the ligamentum Patellæ (LP) and the Patella (P) of the knee joint were insufficient. The aim of the present work is to study some histological changes in the prenatal developing synovial membrane, ligamentum Patellæ (LP) and the Patella(P) of the human knee joint , with special reference to the prenatal developing mechanoreceptors in the synovial membrane stained with Mallory triple stain and additional method, the silver impregnation .That is done to bring about more clear insight of some knee structures , and then better management and treatment of knee lesions and diseases .That was also to fulfill suret el thareate 21,suret Fusilate 53.

Material & Methods:

33 Human (male and female) fresh fetuses aged 4 months (13-16wks-CRL 9-14cm) , and 9 months(full term) :(33-36 weeks) CRL 31-34cm)and newborn infant (37-38 weeks) CRL 35-36cm) ,besides four adult male and female knee joints for comparison were used in this study. The fetuses were collected from the miscarriage and spontaneous abortion, with no apparent lacerations or abnormalities obtained from Gynecology and Obstetrics Department Al -Zharaa hospital-Cairo - Egypt (according to medical ethics). They were used for the study some changes of the developing prenatal normal morphogenesis and histogenesis of the synovial membrane (stratum synoviale) (SM), the ligamentum Patellæ (anterior ligament) (LP), and the Patella (P) of human knee joint. Dissection of both sides of the developing knees was done according to Romanes (2000) in three stages: a) to expose the outermost structures of the joint's cavity, by cutting across the

quadriceps tendon immediately proximal to patella. Then the latter was turned downwards. followed by displacement of the capsule; b) A deeper dissection was done to expose the intraarticular structures, by removing the infrapatellar synovial fold and fat, then the infrapatellar bursa was opened. c) A clear view of the upper surface of the tibia was obtained after cutting across the fibular and tibial collateral ligaments, the arcuate ligament, tendon of popliteus and the remains of the fibrous capsule. Followed by cutting across the cruciate ligaments. Finally the femur was removed. Then specimens were fixed in formalin. To illustrate the morphology of the developing knee joints, photos were photographed by Canon camera zoom. For histological study, specimens from of parts`of the synovial membraneSM of 4 months fetuses :(33-36 weeks) CRL 31-34cm) and full term :(33-36 weeks) CRL 31-34cm) and ligamentum Patellæ LP,and the patella P of full term were collected freshly and fixed in formalin for 10 days, then dehydrated, cleared in benzene, embedded in paraffin wax, cut serially at 7 microns thickness and stained with haematoxylin and eosin stain for detection of general histological structures, Mallory's stain to investigate collagenous tissue ,Masson trichrome stain for evaluation of collagenous tissue,Van Gieson to illustrate collagen and elastic fibers . Mallory triple stain can illustrate nerve endings and neuroreceptors (mechanoreceptors)in the synovial membrane ,besides silver impregnation –Gordon and Sweet to illustrate neuroreceptors and free nerve endings.(Drury &Walington, 1980). The CRL of each fetus was obtained and then converted into weeks of menstrual prenatal ages according to tables of Sadler (2012) and Abdelwahab et al. (2018)

Results:

Morphological Results:

Morphological examination of the knee joint anterior view full flexion position of 4 month fetus (13-16wks-CRL 9-14cm) showed part the small sized knee joint as the lower end of the femur articulated with the tibial condyles .The cavity of the knee had an intra articular septum. Small cartilaginous patella was seen. Fig A. the patella was small cartilagenous, no fat was seen around the patella.

The ligamentum Patellæ (anterior ligament) was the central portion of the common tendon of the Quadriceps femoris, whichwas continued from the patella to the tuberosity of the tibia around it.

Morphological examination of the overview of the left leg of a full term fetus (33-36 weeks) CRL 31-34cm anterior view showed that the upper surface of tibia beared the menisci. Parts of Synovial membrane and its reflection and synovial plica were seen. The pattella and ligamenetum patellea were seen (Figs. Aa&A-b

The long diameter of the lateral meniscus was 8mm, and the medial meniscus was 7mm The long diameter of the patella was 11mm and the transverse diameter was 9 mm.

There were two areas seen in theposterior surface of the patella: small lower part with more cartilaginous appearance and an upper part with more firm consistency and with bony appearance.The patella and infra pattellar pad of fat were seen forming fatty ring that extended around the patellar margins. after the ligamentuml patellea was cut and reflected. Fig .A-b .Synovial reflection and synovial plicae in the form of two thin cords were seen

The medial meniscus had an inner border adjacent to the intercondylar area of the upper surface of the tibia and an outer border at the periphery and attached to the capsule of the joint and its medial collateral ligaments. It lied beneath the fat pad

Morphological examination of the left knee of newborn infant (37-38 weeks) CRL 35-36cm), anterior aspect in full flexion position showed the medial condyle and the lateral condyle of the femur and the intercondyler area with intact differentiated cruciate and menisco- femoral ligaments. The upper surface of the tibial condyles of the knee joint were in articulation with the condyles of the femoral. The capsule around the knee joint and Synovial membrane was seen around the kneejoint (Fig. A-c).

Morphological examination of the right knee joint showed presence of large amount of fat inside the infra patellar fold , and alar folds, and also the patelIa was attached to quadriceps tendon Fig. (Ad): of full term after further dissection showed that the intra articuLar septum was between the medial and lateral condyle and was differentiated into three bands, posterior and anterior cruciate ligaments and menisco femoral .The fibular collateral ligament, and the well-developed capsule as well as ligamentum patellae (Fig. A-e):

Morphological examination of the knee joint of a full term fetus (33-36 weeks) CRL 31-34cm posterior view full flexed position showed the oblique popliteal ligament was an expansion of the semi membrenosus tendon, which supported the capsule of the keen joint posteriorly and lateraly. Fig A-f.The oblique popleteal ligament was well defined thickness across the poster medial aspect of the capsule, and was an extension from the tendon of insertion of semimembranosus.

Morphological examination of a left adult Human knee joint anterior aspect in full flexion position showed marked asymmetry of the femoral condyles and marked projections of the lateral edge of the patellar surface of the femur. The big patella was bony attached to quadriceps tendon .The quadriceps tendon was sectioned and the patellar flap retracted distally (Figs. B-a and Fig. B-b).

After further dissection the knee joint of Fig. (-B a) showed a thick well developed lateral meniscus and medial meniscus, the anterior cruciate and posterior cruciate ligaments, and the menisco femoral ligaments. The patella was attached to quadriceps tendon.

Histological results:

Histological examination of serial sections stained by H&E of part of T.S of part of the intra articular septum of (4 month fetus 13-16wks-CRL 9-14cm) (Figs 1-a,&c) showed part of the mesenchyme represent in two centers that will form the future synovial membrane and cartilaginous tissue of menisci and the ligaments (Fig 1- a).

Higher magnification of part of the mesemchymal center and tissue around showed part of the mesenchymal tissue containing blood vessels and the next inner cartilaginous tissue was differentiated into two strata: an outer deeply PINK stained stratum and an inner lightly stained stratum red.Some cells showed twin appearance Fig 1-b.

Fig. (1-C) higher magnification of part of the previous photo stained by Mallorys triple stain showed the peripheral mesenchymal tissue containing blood vessels and the next inner cartilaginous tissue was differentiated into two strata: an outer (O) deeply BLUE stained stratum and an inner lightly stained stratum. The nuclei of the cells stained red. Some cells showed twin appearance.

Histological examination of serial sections stained by H&E of part of T.S of part of the synovial membrane of (4 month fetus 13-16wks-CRL 9-14cm) (Figs. 2a &b) showed part the synovial membrane was formed of intima, subintima and deep synovial tissue. The intimal layer was discontinuous formed of synoviocytes with different size and shape arranged in 2-5 cell layers.. The subintimal layer was full of fibroblasts and fine collagen fibers present in ground substance. There was no basement membrane between the intimal and subintimal layer. Some villi (V) formed from the synoviocytes were seen (Fig. 2a). The subintimal layer was full of numerous fibroblasts and short collagen fibers. The villi formed from the pleomorphic synoviocytes arranged in 2-5 layers (Fig 2-b).

Histological examination of serial sections stained by of part of T.S of part of the synovial membrane of stained by Masson trichrome of 4 month fetus(13-16wks-CRL 9-14cm) showed the subintimal layer contained numerous fibroblasts , areolar C.T.tissue with fat cells and thin short collagen bundles and many blood vessels (Figs. 2-c & 2-d). Few lymphocytes and macrophages were noted.

Histological examination of serial sections of part of T.S of part of the synovial membrane stained by Mallory triple stain of 4 month fetus(13-16wks-CRL 9-14cm) showed the deep subintimal areolar C.T. layer containing fibroblasts ,thin short collagen bundles ,and kinking blood vessels and numerous capillaries . The wall of the artery was developed with internal elastic lamina IEL with wavy line and thick wall with wide non collapsed empty lumen. The wall of the capillary was formed of single layer of endothelium and contained blood cells. Undifferentiated mesenchymal cells similar to fibroblasts with smaller size and macrophage were seen Fig. (3):

Lymphocyte with large basophilic nucleus. Free nerve endings around the blood vessel and Ruffini-like neuroreceptor with dendritic ramifications and the button like endings were noted.

Pacini corpuscle with lamellea of cells showing onion like structure, the connective tissue capsule was continuous with the endoneurum. The perineural epithelium contained some blood capillaries (Fig. 3).

Histological examination of serial sections of part of T.S of part of the synovial membrane of full term human :(33-36 weeks) CRL 31-34cm) stained by H&E showed that the synovial membrane was formed of intima, subintima and deep synovial tissue. The intimal layer was formed of one layer of synoviocytes .The subintimal layer had fibroblasts, macrophages and short collagen bundles (No basement membrane was present between intima and subintima (Fig. 4)

Histological examination of serial sections of part of T.S of part of the synovial membrane stained by Mallory triple stain of full term human (33-36 weeks) CRL 31-34cm) showed the parallel more dense collagen bundles and elastic fibers than the previous age.The deep sub synovial was formed of special organized collagen bundles The synovial tissue that was full of numerous large blood vessels (Fig.4a).

Histological examination of serial sections of part of T.S of part of the synovial membrane of full term human (33-36 weeks) CRL 31-34cm) showed that the collagen bundles were parallel more dense than the previous age.The deep sub synovial layer was formed of special organized collagen bundles of the synovial tissue that was full of numerous large branched blood vessels and .Some capillaries were fenestrated ,other capillaries had no fenestration abd contained blood cells . Nissls granules of mast cells were seen dispersed near the blood vessels.

The walls of the capillaries were formed of single layer of endothelium. The vein was collapsed (Fig.4b).

Histological examination by light microscope of serial sections stained with Mallory tripe stain (Fig.4c) of part of the deep synovium of full term human:(33-36 weeks-CRL 31-34cm)illustrated part of the deep subintimal layer containing wide spaces. Giant cells with podia and ruffled cytoplasm having different shapes and size secreting collagen in the extra cellular matrix ECM were seen. Fibroblasts, thin wavy elastic fibers, undifferentiated mesenchymal cells

(UMC) were noted. Excess collagen was excreeted from the giant cells masked some giant cells. Thick and thin Collagen was excreted from the giant cells. Fibroblasts synoviocytes with cytoplasmic extension were seen. Macrophages were noted. Thicker longer darkly stained collagen bundles than the previous age were noted (Fig .4c)

Histological examination by light microscope of serial sections stained with Masson trichrome of of part of TS of the synovial membrane of full term human:(33-36 weeks- CRL 31-34cm):showed that the sub intimal layer contained few , fibroblasts(f) ,increased elastic fibers(E) and thicker collagen bundles (B) than the previous age and blood vessels with many dispersed granules of most probably mast cell (Fig. 4d).

Histological examination by light microscope of serial sections stained with silver impregnation – Gordon and Sweet of TS of part of the synovial membrane of full term human:(33-36 weeks) CRL 31-34cm):showed that two Pacinian corpuscles with core and cells arranged in lamellar near the blood vessel ., were seen .Free nerve endings FNE Fig (4-e) were noted.Besides encapsulated elongated oval structures resemble Meissners corpuscle endings were observed . The Meissners corpuscle were covered by thin CT capsule and had a nerve fiber ran zigzag torous or spiral inside the capsule giving the corpsule a striated appearance, and some had more than one axon . Rafini like structure with button endings were noted. (Fig. 4-e)

Histological examination by light microscope of serial sections stained with silver impregnation – Gordon and Sweet of TS of part of the synovial membrane of full term human:(33-36 weeks) CRL 31-34cm) showed many encapsulated Ruffini endings displayed dendritic ramifications with expanded terminal buttons

More than one Pacini corrpusle near the blood vessel were seen. Meissensr like corpuscles with zigzag and spiral like appearance and free nerve endings were observed. FNE (Fig 4-f)

Histological examination by light microscope of serial sections stained with silver impregnation – Gordon and Sweet of TS of part of the synovial membrane (Fig (4-g)) of full term human :(33-36 weeks) CRL31-34cm): showed long single encapsulated structures resembled Golgi tendon organ. Thestructures resembled Golgi tendon organ, composed of Capsule .periaxial space surrounded multiple inner large components .The presence of fusiform structure with single axon and free nerve endings (FNE) were noted .T he presence of many SPIRAL and ZIGZAG nerve endings similar to Meissner Corpuscle were seen (Fig. 4-g):

The ligamentum patelle and the patella of the full term human :(33-36 weeks) CRL 31-34cm):

Histological examination of serial sections of part of ligamentum patelle full term:(33-36 weeks) CRL 31-34cm): stained by Van Gieson stain (Fig 5) and Masson trichrome stain. Fig.(6) showed long thin collagen bundles arranged in different directions interlacing regularly with elastic fibers with curved ends regularly (Figs. 5&6)

Histological examination of serial sections of part of the growing patella of the full term human:(33-36 weeks) CRL 31-34cm): stained by Van Gieson stain showed two areas differently stained with VanGeison stain and two types of tissues : one stratum was cartilaginous tissue with light stain contained large chondrocytes with different size and few short fine collagen bundles. Some chondrocytes showed the twin appearance. Another stratum was fibro cartilaginous tissue heavily stained brown contained thick short and long collagen fibers and fewer small chondrocytes found between the collagen (Fig. 7):

- The growing patella showed the interstitial growth: growth from inside in the lightly stained area (hyaline cartilage, and The appositional growth (growth from outside (dark stratum) ; occurred in the CT pericondrium
- the interstitial growth :growth from inside in the lightly stained area (hyaline cartilage), In the interstitial growth :growth from inside single cell had a capsule, when it divided into two ,each daughter cell had its own capsule ,the primary capsule disappeared and the two cells remained close to each
- The appositional growth (growth from outside (dark statum); occurred in the CT pericondrium: New layers of cartilage were added from the inner condrogenic layer of the perichondrium: where undifferentiated mesenchymal cells UMC formed chondrocytes(cartilage cells).

Histological examination by light microscope of TS serial sections stained with Van Gieson of part of the synovial membrane of the prenatal developing human knee joint of full term (33-36 weeks- CRL 31-34cm):showed that part of the capsule was formed of dense interlacing wavy parallel and long thick collagen bundles .The capsular tissue was continues with part of the synovial tissue that had blood vessels and capillaries full of blood cells (Fig. 8). The elastic fibers were wavy very thin and stained yellow, meanwhile collagen stained brown and were ribbon like

Photos:
A-Morphological photos

Fig.A :Aphotograph of the knee joint anterior view full flexion positionof 4 month fetus (13-16wks-CRL 9-14cm) showing part the lower end of the femur and the intercondyler area and the of intra articular septum septum genu ,Note the tiny foramena oh the sides of the septum.

Note the very smallcartilagenous patella (arrow) and no fat is seen around it.

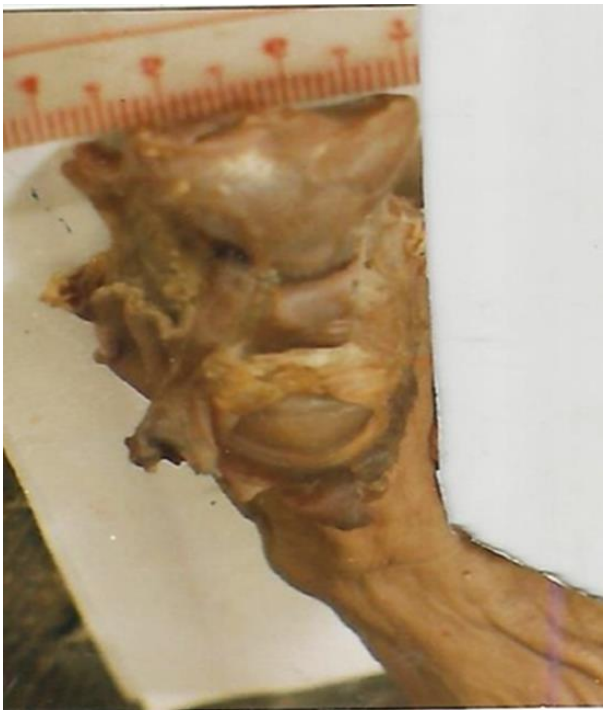

Fig.Aa: A photograph of overview of the left leg of a full term fetus (33-36 weeks) CRL 31-34cm anterior view showing the upper surface of tibia bearing the menisci. Parts of Synovial reflection and synovial plica.

The pattella and ligamenetum patellea are seen. The long diameter of the lateral meniscus is 8mm-,and the medial meniscus is 7mm The long diameter of the patella is 11mm and the transverse diameter is 9 mm. There is two areas are seen in the inner surface of the patella: small lower part with more cartilaginous appearance and an upper part with more firm in consistency and with bony appearance. A-b photograph of the leg of a full term fetus (33-36 weeks) CRL 31-34cm anterior view showing t he patella (arrow)and infra pattellar pad of fat (head arrow)are seen forming fatty ring that extended around the patellar margins after the ligamentuml patellea is cut and reflected. Note the circumferential extra synovial Parts of Synovial reflection and synovial plicae as two thin cord (star) are seen medial (M)and lateral (L)menisci are seen. The medial meniscus has an inner border (i) adjacent to the intercondylar area of the upper surface of the tibia and an outer border (o)at the periphery and attached to the capsule of the joint and its medial collateral ligaments .It lied beneath the fat pad

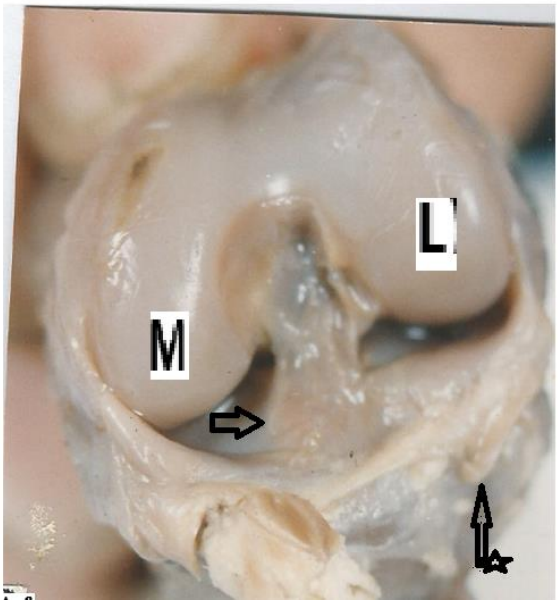

Fig. (A-c): A photograph of left knee of newborn infant (37-38 weeks) CRL 35-36cm) ,anterior aspect in full flexion position showing the medial condyle (M)and the lateral condyle(L) of the lower end of the femur and the intercondyler area with intact differentiated cruciate and menisco- femoral ligaments (arrow).The upper surface of the tibial condyles of the knee joint are in articulation with the condyles of the lower ends of the femur. Notice the capsule around the knee joint and Synovial lining are seen (arrow-star)..

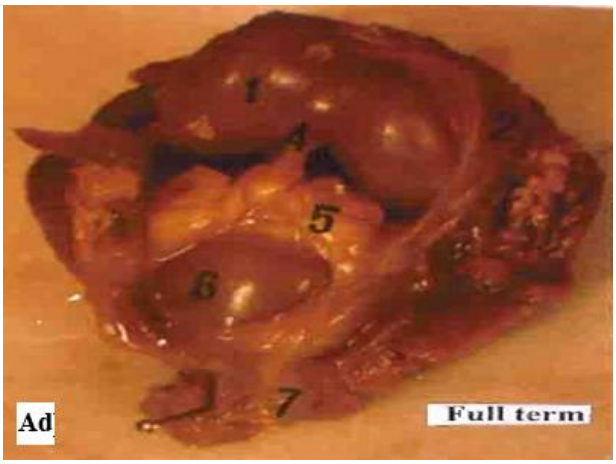

Fig. (A-d): A photo of the right knee joint of full term (33-36 weeks) CRL 31-34cm showing the lateral condyle (I) projects less than the media condyle (2). Notice the presence of large amount of fat inside the infra patellar fold (4) and alar folds (5) and also the patelIa (6) is attached to quadriceps tendon (7). Parts of Synovial reflection and synovial plica are seen

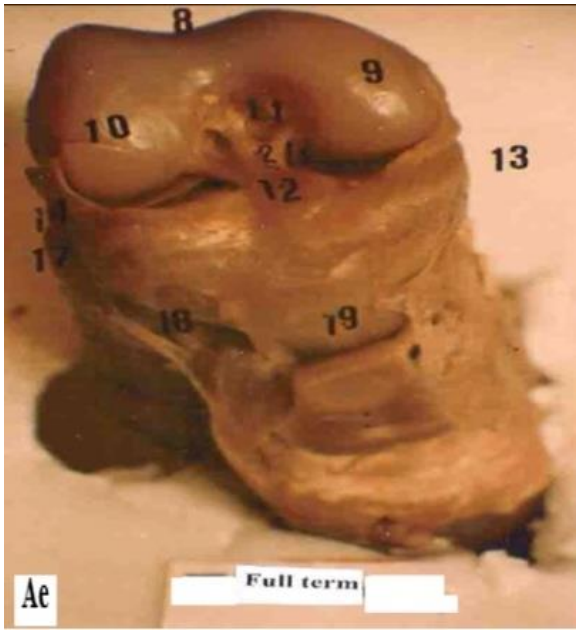

Fig. (A-e): A photograph of the same previous joint Fig. (A-d) after further dissection showing that the intra articuLar septum is between medial (9) and lateral condyle (10) and is differentiated into three bands, posterior (11) and anterioi (12) cruciate ligaments and menisco femoral ligament (21). Notice the slight projection of lateral edge of the patellar fossa (8) and notice also the coronary ligament (13) the lateral meniscus (N), the fibular collateral ligament (17), and the well-developed capsule (18) as well as ligamentum patellae (19).

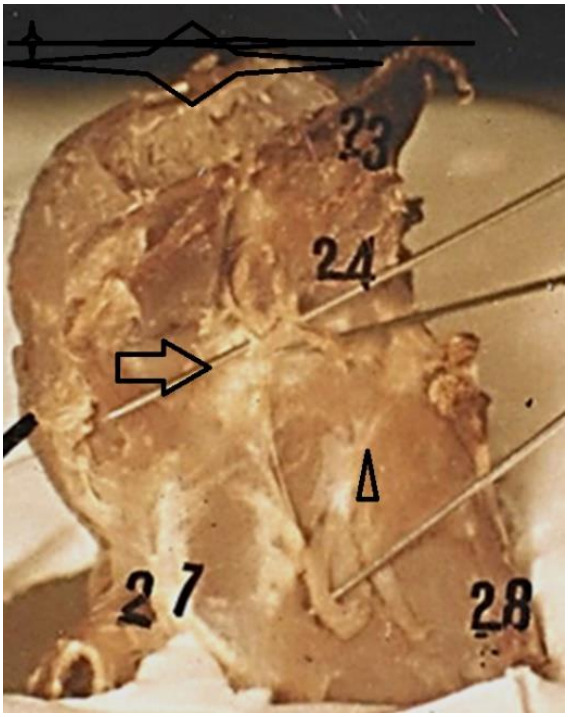

Fig A-f: photograph of the knee joint the of a full term fetus (33-36 weeks) CRL 31-34cm posterior view full flexed position showing the oblique popliteal ligament is an expansion of the semi memb renosus tendon, which supported the capsule of the keen joint posteriorly and lateraly.

The oblique popleteal ligament is well defined thickness across the poster medial aspect of the capsule, and is an extension from the tendon of insertion of semimembranosus.

The semimembranosus insertion sends a fibrous expansion upward and laterally, to reinforce the capsule on the back of the knee joint. The expansion is called the oblique popleteal ligament arcuate ligament, (headarrow) the popliteus muscle (28).

On either side of the joint, the synovial membrane passed downward from the femur, lining the capsule to its point of attachment to the menisci; it might then be traced over the upper surfaces of those to their free borders, and thence along their under surfaces to the tibia. At the back part of the lateral meniscus it formed a cul-de-sac between the groove on its surface and the tendon of the Popliteus; it was reflected across the front of the cruciate ligaments, which were therefore situated outside the synovial cavity.

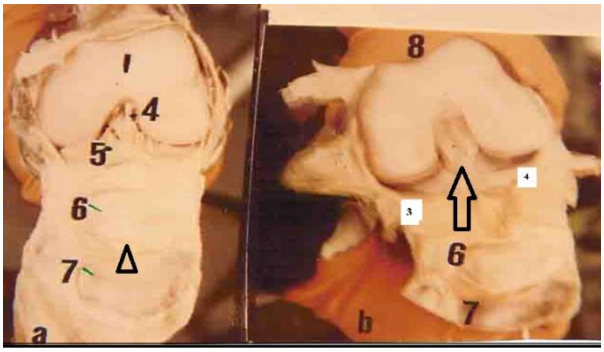

Fig. (Ba): A photograph of the left adult human knee joint anterior aspect in full flexion position showing marked asymmetry of the femoral condyles and marked projections of the lateral edge of the patellar surface of the femur (1). Notice the big bony patella (arrow head) (6) is attached to quadriceps tendon (7) the quadriceps tendon is sectioned and the patellar flap retracted distally Fig. (B-b): A photograph of previous knee joint of Fig. (-B a) after further dissection showing the thick well developed lateral meniscus (3) and medial meniscus (4), the anterior cruciate) and posterior cruciate ligaments , and the menisco femoral ligaments (arrow) and the patella (6) is attached to quadriceps tendon (7).

Histological photos:

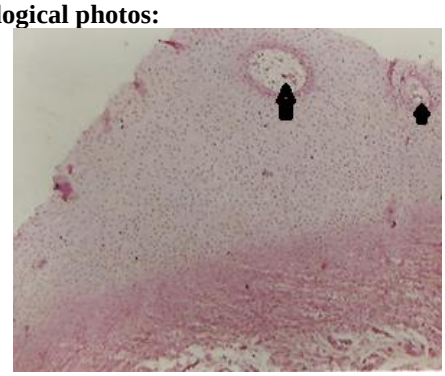

Fig. (1-a): Photomicrograph of part of T.S of part of the intra articular septum of (4 month fetus 13-16wks-CRL 9-14cm) showing part of the mesenchyme represented in two centers of chondrification (arrow)that will form the future synovial membrane and cartilaginous tissue of menisci and the ligaments, H&EX400.

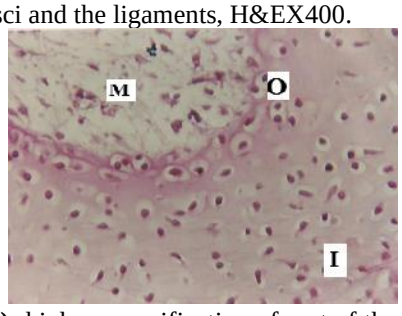

Fig (1-b): higher magnification of part of the previous photo showing peripheral mesenchymal tissue (M) containing blood vessels(v) and the next inner cartilaginous tissue is differentiated into two strata : an outer (O)deeply PINK stained stratum and an inner lightly stained stratum (I) red.Some cells showed twin appearance, H&EX1000.

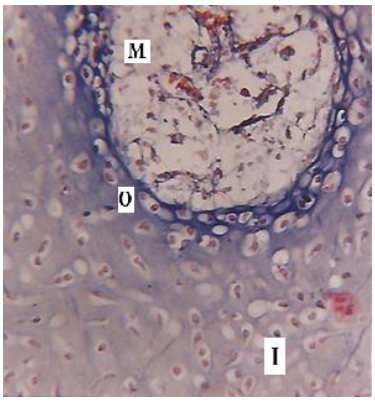

Fig. (1-C): Higher magnification of part of the previous photo showing peripheral mesenchymal tissue (M) containing blood vessels (v) and the next inner cartilaginous tissue is differentiated into two strata: an outer (O) deeply BLUE stained stratum and an inner lightly stained stratum (I), the nuclei of the cells stained red. Some cells showed twin appearance .Mallorys triple stain x1000.

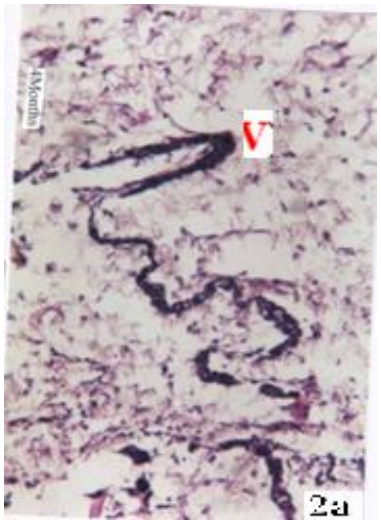

Fig 2 a): Photomicrograph of part of T.S of synovial membrane of 4 month fetus(13-16wks-CRL 9-14cm) the synovial membrane is formed of intima ,subintima and deep synoviual tissue. Showing the discontinuous intimal layer of synoviocytes with different size and shape. The synoviocytes are arranged in 2-5 cell layers(arrow). The subintimal layer is full of fibroblasts and fine collagen fibers present in ground substance .Note that there is no basement membrane between the intimal and subintimal layer. Note that some villi (V) formed from the synoviocytes are seen (H&E x l00)

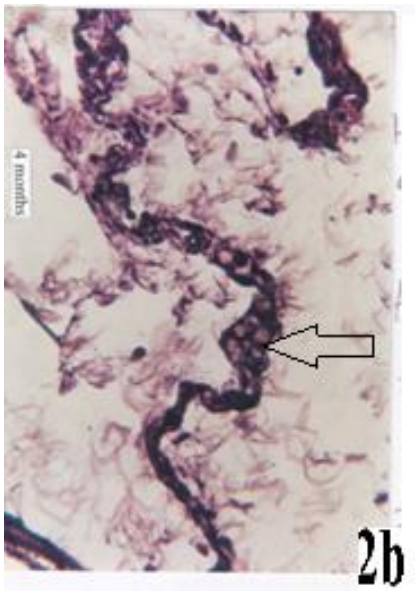

Fig 2-b): Higher magnification of part of the prevois photo showing Photomicrograph of part of T.S. of part of synovial membrane of 4 month fetus(13-16wks-CRL 9-14cm) showing the discontinuous intimal layer of synoviocytes with different shapes. The subintimal layer is full of numerous fibrobasts and short collagen fibers. Note that there is no basement membrane between the intimal and subintimal layer. Note the villi formed from the synoviocytes. Note the pleomorphic synoviocytes arranged in 2-5 layers (H & Ex 1000)

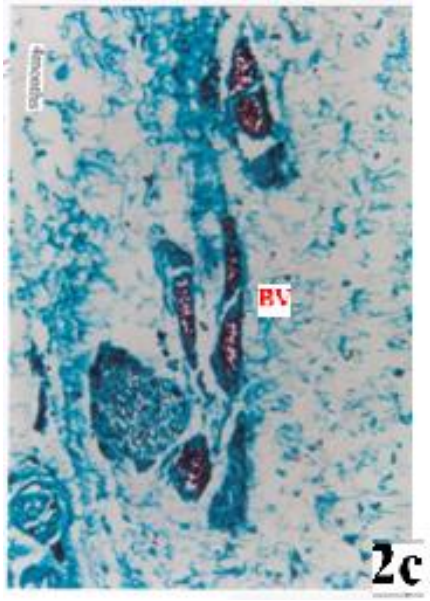

Fig (2-c): Photomicrograph of part. of the synovial membrane of 4 month fetus(13-16wks-CRL 9-14cm) showing the subintimal layer containing numerous fibroblasts(f) , areolar C.T.tissue((arrow) with fat cells and thin short collagen bundles and many blood vessels.Masson trichrome x100

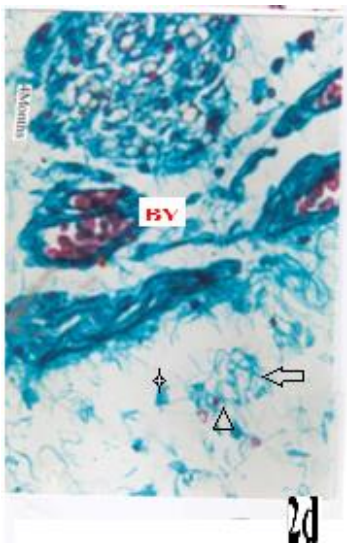

Fig (2-d): Higher magnification of part of the previous photo showing Photomicrograph of part of the synovial membrane of4 month fetus(13-16wks-CRL 9-14cm illustrating the subintimal areolar C.T.layer containing numerous fibroblasts (f) (arrow) ,fat cells,few lymphocytes(head arrow) macrophages (star)and short collagen bundles and blood vessels and capillaries containing blood cells. (BV) Masson trichrome x 1000

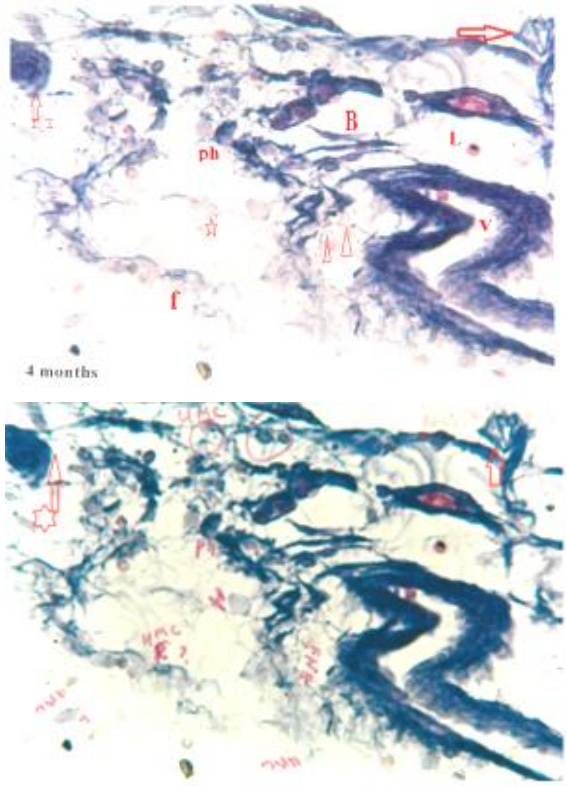

Fig. (3): Photomicrograph of part of L.S. of synovial membrane of 4 month fetus(13-16wks-CRL 9-14cm) showing the deep subintimal areolar C.T. layer

containing fibroblasts (f) ,thin short collagen bundles (B)and kinking blood vessels,(v) and numerous capillaries(c). The wall of the artery is developed with internal elastic lamina IEL wavy line and thick wall with wide non collapsed empty lumen .The wall of the capillary is formed of single layer of endothelium and contained blood cells. The areolar C.T. contained collagenous, elastic and macrophage (ph).
Note the undifferentiated mesenchymal cells similar to fibroblasts with smaller size (star).
Note the lymphocyte (L) with large basophilic nucleus.
Note the free nerve endings around the blood vessel (head arrow). Note Ruffini -like neuroreceptor with dendritic ramifications and the button like endings of the .(arrow)
Note the Pacini corpuscle with lamellea of cells showing onion like structure (arrow star), the connective tissue capsule is continuous with the endoneurum. Perineural epithelium containing some blood capillaries. Mallory triple stain x 1000

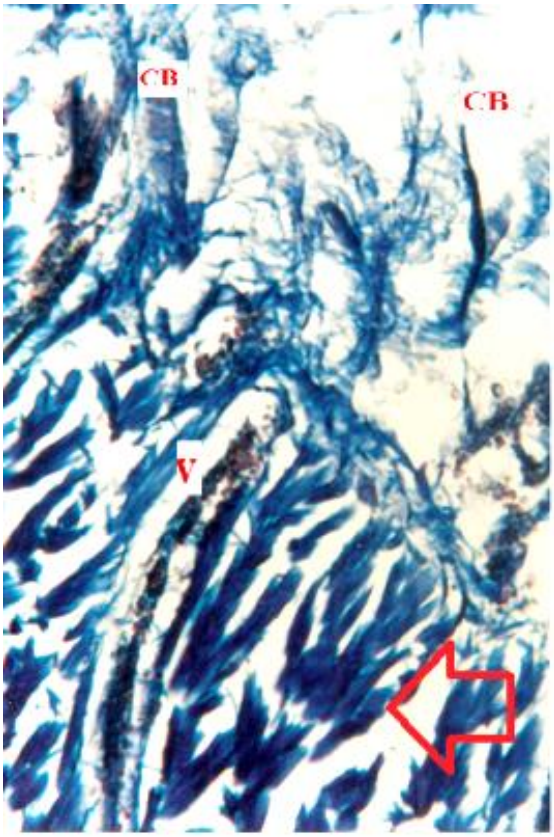

Fig (4): Photomicrograph of part of TS of part of the synovial membrane of full term human :(33-36 weeks) CRL 31-34cm): showing that the synovial membrane is formed of intima, subintima and deep synoviual tissue. The intimal layer is formed of one layer of synoviocytes .The subintimal layer has fibroblasts (f), macrophages (ph) and short collagen bundles (arrow). No basement membrane is present between intima (I) and subintima (SI) H&E x1000

Fig.4a): Photomicrograph of T.S. of part of synovial membrane of full term human (33-36 weeks) CRL 31-34cm) showing the parallel more dense collagen bundles (CB) and elastic fibers than the previous age.
Note :the deep sub synovial is formed of special organized collagen(arrow))bundles of the synovial tissue that is full of numerous large blood vessels(v), Mallory triple stain x 1000.

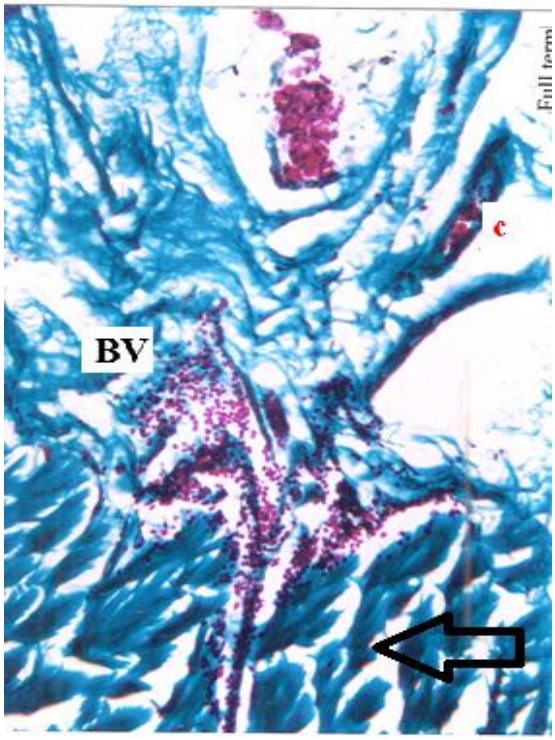

Fig. (4b): Photomicrograph of T.S. of part of synovial membrane of full term human (33-36 weeks) CRL 31-34cm) showing the parallel more dense collagen bundles than the previous age.. Note :the deep sub synovial layer is formed of special organized collagen bundles(arrow) of the synovial tissue that is full of numerous large branched blood vessels(BV)and Some capillaries are fenestrated(arrow star), some capillaries are complete with no pores with blood cells (c). Nissls granules of mast cells are seen (dispersed near the blood vessels.
Note that the walls of the capillaries are formed of single layer of endothelium. .The vein is collapsed (arrow head) .Masson trichrome x 1000.

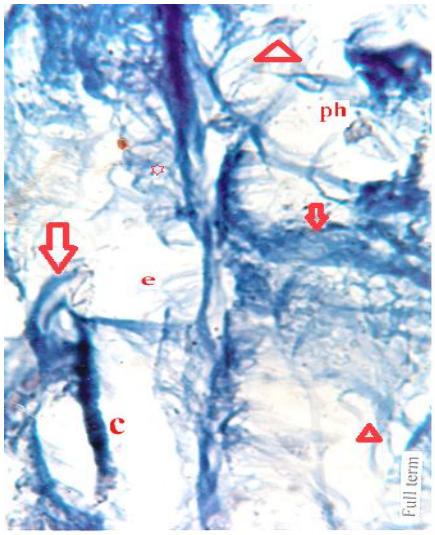

Fig (4c): Photomicrograph of part of TS of part of the deep synovium(subsynovial) membrane of full term human:(33-36 weeks-CRL 31-34cm): showing the deep subintimal layer containing wide spaces and many.Giant cells with podia and ruffled cytoplasm and `different shapes and size (arrow) are seen excreting collagen in the extra cellular matrix ECM.
Note the excess collagen bundles excreted and close to the giant cells, some times the excess collagen masked the giant cells .Collagen bundles branch and form network Fibroblasts ,synoviocytes with cytoplasmic extension (head arrow) are seen . Macrophages are seen (ph).Thin wavy elastic fibers (e) and thicker longer darkly stained collagen bundles (c) than the pervious age .
Note the undifferentiated mesenchymal cells(UMC) (star). Mallory triple stain x 1000..

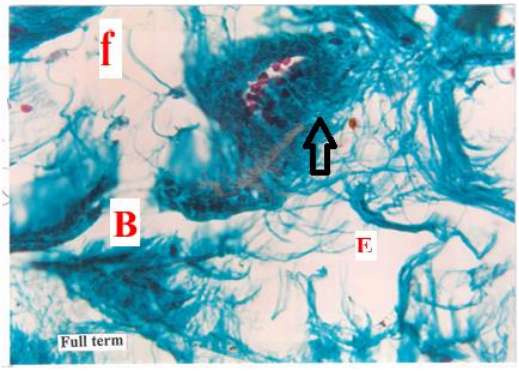

Fig. (4d): Photomicrograph of part of TS of part of the synovial membrane of part of full term human :(33-36 weeks) CRL 31-34cm): showing the sub intimal layer containing few , fibroblasts(f) ,increased elastic fibers(E) and thicker collagen bundles (B) thick collagen bundles than the pervious age and blood vessels with many dispersed granules of most probably mast cell(arrow) Masson trichrome x 1000.

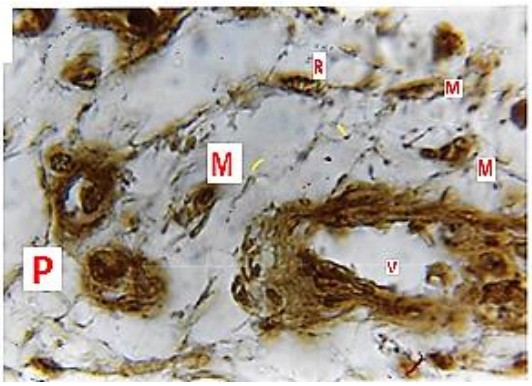

Fig (4-e): Photomicrograph of part of TS of part of the synovial membrane of part of full term human:(33-36 weeks) CRL 31-34cm): showing many encapsulated elongated oval structures resemble Meissners (M) corpuscle endings . The corpuscle is covered by thin CT CAPSULE and has a nerve fiber runs zigzag or spiral inside the capsule giving the capsule a satriated appearance and has more than one axon .
Note the Rafini like structure with button endings (R).
Two large Pacinian corpuscles (P) are seen near the blood vessel (V), one axon extended from the capsule .
Note the communication between the encapsulated receptors.
Note the presence of free nerve endings FNE(yellow line).
Gordon and Sweet Silver impregnation x1000

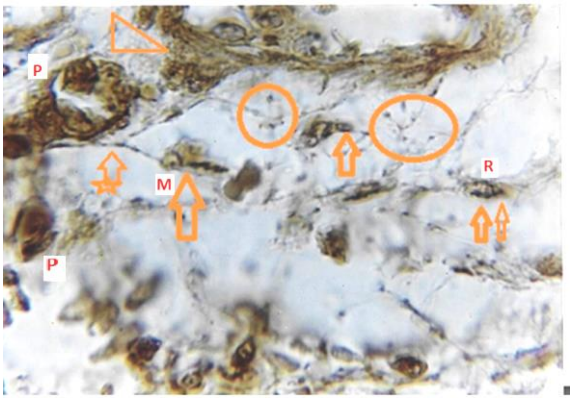

Fig. (4-f): Photomicrograph of part of TS of part of the synovial membrane of part of full term human:(33-36 weeks) CRL 31-34cm): showing many encapsulated structures resemble Raffini with branched nerve corpuscle) endings Ruffini endings display dendritic ramifications with expanded terminal buttons (R)
More than one Pacini corrpusle near the blood vessel is seen (P)
Note the zigzag and spiral like arrangement of nerve ending inside the Meissensr like corpuscles (M)
Free nerve endings (FNE)around Part of blood vesel are seen (V)

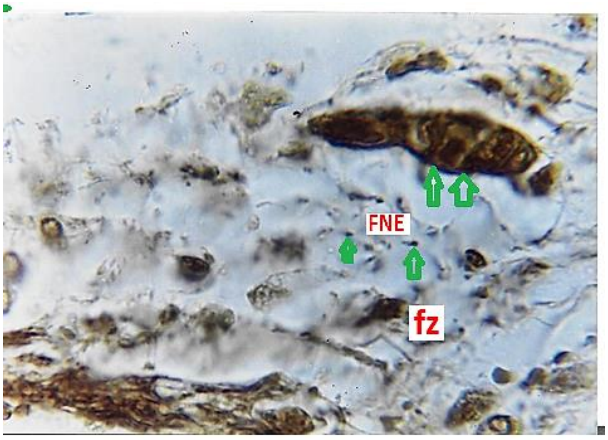

Fig. (4-g): Photomicrograph of part of TS of part of the synovial membrane of full term human:(33-36 weeks) CRL 31-34cm): showing many long single encapsulated structures resemble s Golgi tendon organ . (G)double arrows) ,composed of Capsule .periaxial space surrounded and multiple inner large components
Note the fusiform (fz) structure with single axon. Note the presence of ,many free nerve endings (FNE) Note the presence of many SPIRAL and ZIGZAG nerve endings similar to Meissner Corpuscle (M)with axon Gordon and Sweet Silver impregnation x1000

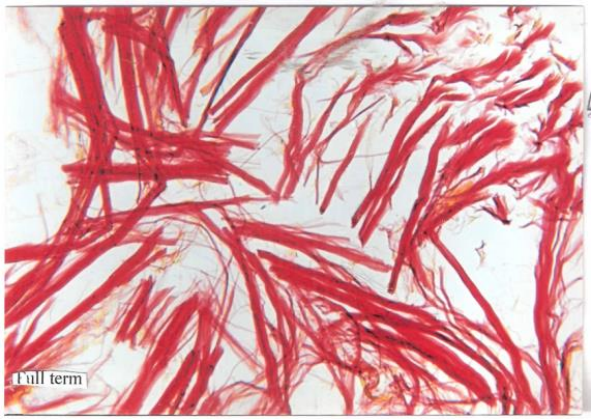

Fig (5): Photomicrograph of TS of part of ligamentum patelle of the full term human :(33-36 weeks) CRL 31-34cm): showing long thin collagen bundles \interlacing regularly arranged in different directions. Van Gieson x 1000

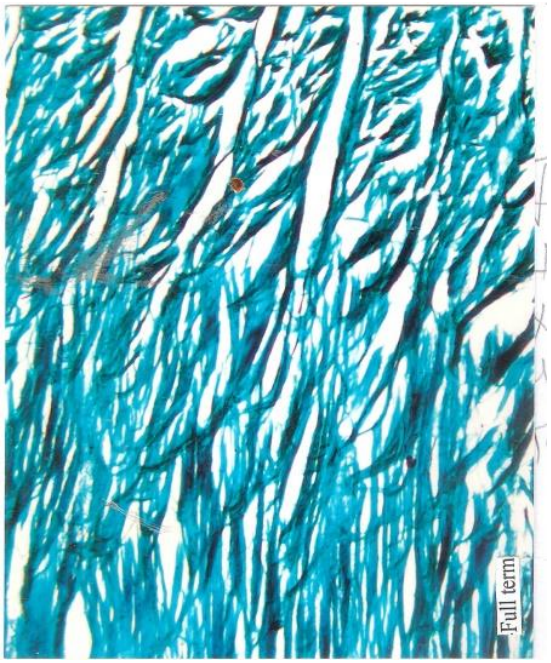

Fig (6): Photomicrograph of TS of part of ligamentum patelle of the full term human :(33-36 weeks) CRL 31-34cm): showing long thin collagen bundles \interlacing with elastic fibers with curved ends (arrow)regularly arranged .Branched faciculi are seen, Masson trichrome x 1000.

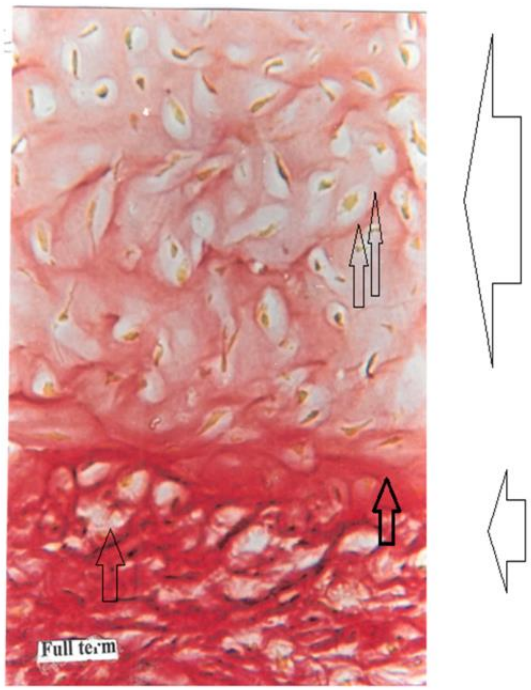

Fig (7): Photomicrograph of part of TS of part of the growing patella of the full term human:(33-36 weeks) CRL 31-34cm): showing two areas differently stained with VanGaison stain with two types of tissues: cartilaginous tissue with light stain and was full of

large chondrocytes with different size and few short fine collagen bundles. Some chondrocytes show twin appearance (double thin arrow). Another stratum is firo cartilaginous tissue heavily stained contained thick long collagen bundles (dark arrow)deeply stained brown and fewer small chondrocytes found between the collagen .

The growing patella shows the interstitial growth :growth from inside in the lightly stained area, and the appositional growth (growth from outside(small arrow –dark stratum) ;the CT pericondrium:New layers of cartilage are added from the inner condrogenic layer of the perichondrium: where undifferentiated mesenchymal cells UMC formed chondrocytes (cartilage cells).

Note that in the interstitial growth :growth from inside : (big arrow- out side the photo : light statum)single cell has a capsule, when it divides into two ,each daughter cell has its own capsule ,the primary capsule disappears and the two cells remained close to each .

Note: the big arrow out side the photo points at the growing hyaline cartilage and how the cells of cartilage multiply.

The small arrow outside the photo points at the pereichondrium, Van Gieson x 1000

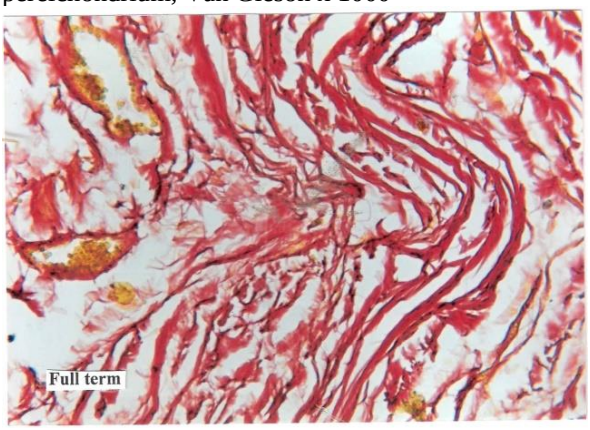

Fig. (8): Photomicrograph of part of TS of part of the synovial membrane of part of full term human :(33-36 weeks- CRL 31-34cm): showing part of the capsule is formed of dense interlacing wavy parallel and longer thick collagen bundles and part of the synovial tissue with blood vessels continuous with the capsule. The elastic fibers are wavy very thin and stained yellow, meanwhile the`collagen bundle are ribbon like and stained brown .Van Gieson x 1000.

Discussion

Morphogenesis:

In the present study morphological examination by the naked eye, of the upper part of the leg of a full term (33-36 weeks) CRL 31-34cm anterior and superior view showed that the lower condyles of the femur articulated with the upper surface of tibia which bearded the medial and lateral menisci. Two thin cords plica of the synovial membrane represented vestigial embryonic remnants were clear. These embryonic remnants, later in the future adult life, if would become hypertrophic, or fibrous, they might produce pain, crepitus, or pseudoblocking. The patella was small cartilaginous in the age of 4month fetus with no fat around it, and had anterior and posterior smooth surfaces with no particular features were seen. The patella became more bony with age progress in the full term fetus. The ligamenetum patellea attached to the quadriceps muscle and enclosed the patella. Theanterior and posterior cruciate ligaments ACL & PCLand the meniscofemoral ligament MFL emerged from the remnant of the intra articular septum (septum genu) (mediastinum genu). The infra patellar pad of fat IPF forming fatty ring (Hoffa's fat pad), extended around the patellar margins was noted in full term fetus.

The results of the present work agreed with Rafael Iñigo Pavlovich (2008) who mentioned that the Knee synovial tissue might hypertrophy or fibrose and resulted in mechanical symptoms that might be mistaken for a meniscal tear or loose body. In particular, synovial vestigial remnants might cause pain or mechanical knee symptoms. The suprapatellar plica was a septum, sometimes fenestrated, might divide the suprapatellar pouch. The medial plical band was noted in approximately 50% of adult cadavers ; while usually asymptomatic, the plica might become taut, hypertrophic, or fibrous and produced pain, crepitus, or pseudoblocking. That medial synovial shelf might then erode the cartilage and caused impingement or medial condyle chondrosis. A careful history and examination could distinguish symptomatic hypertrophy and impingement of Hoffa's fat pad. Synovial impingement was often associated with overload or overtraining. Dysphoria occured during joint line compression where the patient could not explain the exact nature of the sensation and might deny pain but resisted palpation and perceived a feeling of running on the knee.

The results of the present work agreed with Schindler (2014) who reviewed the literature combined with a meta-analysis of studies assessing the outcome of open or arthroscopic plica excision including the author's own series. They mentioned that the term synovial plica described a number of intra-capsular folds thought to represent remnants of a membranous knee joint partition present during fetal development. Although four such folds had been defined, it was mainly the medial patellar plica which had clinical significance as a potential cause of anteromedial knee pain particularly in adolescents. Athroscopic excision of the entire plical fold became indicated in recalcitrant cases and once a plica had undergone irrevocable morphological changes. The procedure carried low morbidity, and the results were universally good

especially if the plica was the sole pathology. Factors associated with a favorable outcome were young patient age, localised symptoms of short duration and absence of plica induced chondromalacia

The results of the present study agreed with Standring et al. (2016) who mentioned that the synovial membrane of the knee was the most extensive and complex in the body. It formed a large suprapatellar bursa between quadriceps femoris and the lower femoral shaft proximal to the superior patellar border. Distal to the patella, the synovial membrane was separated from the patellar ligament by an infrapatellar fat pad. Where it lied beneath the fat pad, the membrane projected into the joint as two fingers alar folds, which bearded villi. The folds converged posterior to form a single infrapatellar fold or plica (ligamentum mucosum), which curved posterior to its attachment in the femoral intercondyler fossa. That fold might be a vestige of the inferior boundary of an originally separated femoropatellar joint. The extent of the infrapatellar plica ranged from a thin cord to a complete sheet that could obstruct the passage of instruments during knee arthroscopy .When sustaintial, it had been mistaken for the anterior cruciate ligament, which was directly posterior to it. The medial plica extended in the midline anteriorly from the medial alar fold medially to the suprapatellar bursa.Occasionally, it could be thickened and inflamed, usually following acute or chronic trauma. The suprapatellar plicae were remenants of an embryonic septum that completely separated the suprapatellar bursa from the knee joint. Occasionally a septum persisted, either in its entirety or perforated by a small peripheral opening. The infrapatellar fat pad was the largest part of a circumferential extra synovial fatty ring that extended around the patellar margins

In the present study histological examination of serial sections of parts of TS of the synovial membrane of 4 month fetus 13-16wks-CRL 9-14cm) stained by H&E and Masson trichrome stain showed that the synovial membrane was formed of intima ,subintima consisted of areaolar tissue and deep synovial tissue. The intimal layer formed of pleomorphic synoviocytes differed in size and shape,some cells simulated macrophages: macrophage-like synoviocytes (MLS): TypeA synoviocytes, and others simulated fibroblasts ; fibroblast-like synoviocytes (FLS) TypeA synoviocytes. The intimal synoviocytes arranged in 2-5 cell layers. The subintimal layer had fibroblasts and fine collagen fibers present in ground substance .No basement membrane between the intimal and subintimal layers was seen. Some villi were formed from the intimal synoviocytes were seen. The subintimal layer stained by Masson trichrome and Mallory triple stain contained fibroblasts, areolar C.T.tissue, fat cells, thin short collagen bundles, many blood vessels and some fenestrated capillaries.

In the present study histological examination of serial sections of parts of TS of the synovial membrane of full term human (33-36 weeks- CRL 31-34cm) showed that the synovial membrane was formed of intima ,subintima and deep synovium.The intimal layer was formed of one layer of pleomorphic synoviocytes:macrophage like synoviocytesMLS and fibroblast like synoviocytes FLS. The subintimal layer had fibroblasts, macrophages, thin elastic fibers, short and long collagen bundles with different thickness. No basement membrane was present between intima and subintima. Macrophages increased in the subintima than the previous age. Parallel dense collagen bundles were thicker, longer than the previous age. Some areas of the deep sub synovium had special organized collagen bundles .The vascularity increased and numerous large branched blood vessels and fenestrated capillaries more than the previous age were noted. Elastic tissue increased than the previous age. The deep subintimal layer contained wide spaces with giant cells having podia and ruffled cytoplasm secreting collagen were seen. Excess collagen bundles close the giant cells, some times masked the giant cells. Different morphologic types of collagen;(long,short ,thick,thin fibril, alone or with elastic fibers, branched, straight, wavy, with specil arrangement) were seen. Type B synoviocytes with cytoplasmic extension were seen. Ncreased macrophages were seen .Thin wavy elastic fibers and thicker longer darkly stained collagen bundles than the previous age were noted.

In the present study ,the presence of the pleomorphic synoviocytes:macrophage like synoviocytes MLS and fibroblast like synoviocytes FLS might contribute in knee diseases if their ratio number disturbed .The increase in macrophages, and blood vascularity with age progress might be due to development of immune system with age progress. That was essential to fulfill the increased need of the developing knee functions. Blood vessels, were active in providing nutrients to both the synovial membrane and the cartilage tissue. Under pathological conditions, synovial macrophages might contribute to cartilage destruction due to prolonged production of proinflammatory cytokines.

The results of the present study agreed with Rafael Iñigo Pavlovich2008 who mentioned that the synovial tissue, of the knee joint, was related to rheumatoid arthritis. However, synovium was a key component in cartilage degradation, overuse syndromes, and impingement syndrome where synovial impingement might mimic a torn meniscus. Synovium might be responsible for nontraumatic knee pain and was sometimes referred to as the “forgotten tissue.”

Rafael Iñigo Pavlovich(2008) pointed that anterior cruciate ligament (ACL) allograft, and ACL autografts once harvested and deprived of their original blood supply, served as scaffolds that underwent cellular repopulate, reorganization, and collagen maturation. Both synovial cells and fibroblast migration resulted in vascularization of the graft from both the femoral and tibial bone tunnels and from the synovial joint lining.

The results of the present study agreed with Smith (2011) who mentioned that the synovial membrane was normally a thin membrane consisting of a lining and a sublining layer of cells. The lining consisted of 1–3 layers of fibroblast-like synoviocytes (FLS) and macrophage-like synoviocytes (MLS) that overlayed the sublining .The lining layer was composed mainly of type III collagen, while the sublining consisted mainly of type I collagen ; In synovitis, the FLS in the lining layer became hyperplastic and the sublining was infiltrated with immune cells The immune cells activated the MLS, which among others produced tumor necrosis factor α (TNFα) and interleukin (IL)-1β, which were potent activators of FLS . Both FLS and MLS had been shown to play key roles in driving the synovial inflammation, both were able to stimulate inflammation and affected the ECM turnover, through the secretion of cytokines, chemokines, and matrix metalloproteinases (MMPs) . However, whether MLS or FLS alone was the main driver of synovitis or they together caused the inflammation was unknown.

In the present study examination of serial sections stained by H&E of parts of the synovial membrane of 4month fetus (13-16wks-CRL 9-14cm) and full term (33-36 weeks) CRL 31-34cm)prenatal showed the presence of intimal velli which increased in size and length with age progress. Areolar tissue with fat cells in the subintima and high vascullariuty in 4month fetus were noted, the vascularity increased with age progress.Alar folds and pad of fat were seen by morphological examination of full term. The pad of fat and synovial membrane were announced recently by Belluzzi et al. (2019) to function as one unit, contributed and involved in some knee and synovial diseases. The increase in velli length, elastic tissue and fat were to accommodate the changed shape and volume of the irregularities of the knee, and worked as cushions during movements. Facilitated low-friction and low-wear articulation filling the synovial cavity, for protection against knee joint damage.

In the present study examination of serial sections stained by Mallory triple stain and Masson trichrome of parts of the synovial membrane of 4month prenatal and full term showed the presence of highly vascular subintima with blood vessels and fenestrated capillaries, free blood cells between the tissues and Nissle granules of mast cells were seen.

The results of the present work agreed with (Ghadially et al.,1983) who mentioned that the internal synovial surface had a small synovial velli which increased in size and number with age .Elsewhere folds and fingers might project into the joint cavity ,some constant enough to be named for example alar folds and ligamentum mucosum of the knee .Accumulation of adipose tissue (articular fat pad)occurred in the synovial membrane in many joints .Such pads,folds,and fingers were flexible elastic and displaceable cushions occupying potential spaces and irregularities in joints which were not wholly filled with synovial fluid during movement. They accommodated to the changed shape and volume of the irregularities. They increased synovial area and might promote distribution of lubricants over articular surface of the intra articular discs and menisci. Synovial velli were normally few, but more numerous where the membrane resisted on the areolar tissue near articular margins and surfaces of folds and fingers. They increased with age and became prominent in some pathological states.

The results of the present work agreed with Smith 2011 who mentioned that capillaries occurred just below or within the intima .Some capillaries were fenestrated and fenestrae tended to face the tissue surface ,while small venules were prominent deeper within the normal synovium. Deeper still in the subintimal layer there were larger venules together with arterioles and lymphatics, forming an anastomosing array. Vessels with lymphatic characteristics were prominent in RA synovium and it had been proposed that failure of lymphatic drainage of synovial fluid might be a cause of villous proliferation in RA synovial tissue. If that was correct, it was likely to be due to over loading of existing lymphatic channels with HA-rich extracellular fluid and leucocytes rather than a lack of lymphatic channels. Apart from the fenestration of superficial capillary endothelial cells there was little evidence of specialization of synovial endothelium. Endothelial cells enlarged in inflamed tissue and microvascular proliferation could occur, but those events were common in inflammation at many sites. Tissue –specific adhesion molecule or "adhressin" had been thought but not evidence of synovium specific vascular markers had been found. However, there remained the possibility that specialized lymphocytes trafficking pathway applied to synovium, possibly based on chemokine –receptors interaction.

The results of the present work were in accordance to Belluzzi et al. (2019) who mentioned that ;the spaces of diarthrodial joints, bursae, and tendon were covered by a specialized mesenchymal tissue, that was, the synovial membrane. From the microscopic point of view, that membrane had two

layers: (a) the intimal and (b) subintimal layer. Typically, in healthy subjects, the cross-sections of the intimal and subintimal layers showed 20-40 mm and up to 5 mm thickness, respectively. However, at many sites there was no discrete membrane, especially where subintima consisted of fibrous tissue or adipose tissue. Belluzzi et al. (2019) added that the intima inner layer was characterized by the presence of one or two sheets of macrophages (type A synoviocytes) or fibroblast-like synoviocytes (type B synoviocytes). Type A synoviocytes were recognizable in the upper part of synovial lining, showing a surface rich in microvilli and microplicae. They were positive for CD163 and CD68 but not for $CD14^{+/lo}$ with a nonspecific esterase activity; typically, they proliferated in inflammatory conditions.

Vascularity of the synovial membrane of the prenatal developing human knee joint and the relation of its changes in knee diseases.

In the present study histological examination of serial sections of part of synovial membrane of 4 month fetus 13-16wks-CRL 9-14cm) and full term human (33-36 weeks) CRL 31-34cm) showed that the subintima had rich microvasculation as there was large branched blood vessels ,some were perpendicular ,others were kinking and numerous capillaries ,some capillaries were fenestrated, which increased with age progress. The vascularity was essential to nourish the knee joint intra-capsular structures, and the transfer of molecules to and from the blood into synovial tissues. Vascularity was necessary to provide healing and repair process of the intra-articular structural lesions in the knee joint. The change in blood vessel architecture, density, stability and maturity might be associated with many knee joint diseases.

The result of the present study agreed with Rafael Iñigo Pavlovich2008 who mentioned that, the synovium was an extremely reactive tissue which played a key roll in the repair process within the knee joint. Proinflammatory cytokines were released in response to intraarticular damage initiating a repair process. In a similar fashion, synovial cell response played a critical role in the healing of meniscal tears. Regardless of whether the tear was in the vascular zone, invasion of Type B synovial cells resulted in a fibroblast-like response enhancing healing.

Vergunst et al. (2005); De Lange-Brokaar et al. (2012) explained that pro-inflammatory cytokines might directly induce neovascularisation or might act by stimulating VEGF production. Among those cytokines, TNF-α, IL-1, IL-6, IL-15, IL-17, IL-18, oncostatin M, macrophage migration inhibitory factor (MIF), granulocyte (G-CSF) and granulocyte-macrophage colony stimulating factors (GM-CSF) were involved in angiogenesis, as well as OA synovitis.

Yves Henrotin et al. (2014) reviewed and discussed the synovial membraneSM vascularization in OA synovitis, to show the recent advances and understanding of: (1) pro-angiogenic phenotype expressed by OA synovial cells; (2) pathways promoting SM angiogenesis in OA; (3) the effects of current drugs on these pathways; and 4) therapeutic perspectives.

That result of the present study agreed with Yves Henrotin, et al.,2014 who mentioned that intra-articular gene transfer of TSP-1 in Wistar rats with OA induced by anterior cruciate ligament transection reduced microvessel density and macrophage infiltration in the synovium, and decreased macroscopic and histologic cartilage lesions (Hsieh et al. 2010). In parallel, IL-1β levels in synovium tissue extracted decreased while transforming growth factor-β (TGF-β) was increased suggesting the involvement of these factors in the TSP-1 effects. Collectively, those data indicated that the local overexpression of an anti-angiogenic factor suppressed synovium inflammation, osteophytes formation and cartilage degradation. That highlighted the key role played by angiogenesis in the OA pathogenesis and that targeting angiogenesis could be a useful strategy to control disease progression.They concluded that angiogenesis played a key role in synovium inflammation and cartilage damage accompanying OA and was critical mechanism in the persistence of OA. Angiogenesis facilitated the invasion of inflammatory cells and increased pain receptors locally. In OA, the SM vascularization process differed from that observed in RA. The blood vessel density and stability and the levels of synovial angiogenesis modulators were higher in RA than in OA. Additional studies were required to identify the specific pathways involved in angiogenesis of OA synovium. Therefore, the inhibition of angiogenesis might control inflammation and pain in OA. Among the currently used pharmacological agents in OA, chondroitin sulphate showed in vitro anti-angiogenic properties mainly by controlling the balance between pro- and anti-angiogenic factors. However, that potential anti-angiogenic effect needed to be confirmed in vitro in a functional model of endothelial cell proliferation and migration and in vivo in OA animal models. Some new molecules were under investigation for their anti-inflammatory and anti-angiogenic properties and they migtht offer a new opportunity to block chronic pain and inflammation in OA.

Belluzzi et al. (2019) pointed that the synovium had a rich microcirculation which allowed the transfer of small and large molecules to and from the blood into synovial tissues. While capillaries occurred just below or within the intima, small venules were prominent within the normal synovium. Still deeper in the

subintimal layer there were larger venules together with arterioles and lymphatics, forming an anastomosing array. Capillaries and postcapillary venules averaged a density of 240/mm^2 . In accordance with what occurred in many other sites, enlargement of endothelial cells as well as micro -vascular proliferation had been observed during inflammation. To date, no specific vascular markers for the inflamed synovial membrane had been found; however, it had been hypothesized the existence of specialized lymphocyte trafficking pathways chemokine-receptor-based.

The importance of involvement of blood vessels in human knee diseases were pointed out by Hsieh et al. (2010); Bainbridge et al. (2007); Lazarus et al. (2008). Who noted PPI-2458, an anti-angiogenic fumagillin analogue, reduced synovitis, bone and cartilage damage in animal models of arthritis It exerted its effects by inhibiting methionine aminopeptidase type 2 (MetAp-2), triggering growth arrest of endothelial cells in the late G1 phase of the cell cycle, inhibiting endothelial cell proliferation and angiogenesis without affecting inflammatory cytokines release (Griffith et al. 1997).

Ashraf et al. (2011) pointed that In OA induced in male Lewis rats by meniscal transection, PPI-2458 reduced synovial and osteochondral angiogenesis, synovial inflammation, cartilage damage, osteophyte size and pain behaviour as evaluated by weight bearing asymmetry (Ashraf et al. 2011). That also suggested that the effects of angiogenesis in inflammation were independent of inflammatory cytokines. Again, that demonstrated the key role played by angiogenesis in OA synovitis, structural damages and pain. Inhibition of angiogenesis therefore offered a potential novel therapeutic strategy for OA.

In the present study, histological study by light microscope of TS of part of the synovial membrane of 4month fetus and full term, showed that the synovial membrane was formed of intima, subintima, and deep synovium. The intima consisted of macrophage like cells and fibroblast like cell,the subintima had excess vascularity ,fibroblasts ,macrophages, few mast cells, elastic fibers and collagen bundles ,and the deep synovium showed special organization of collagen bundles in some areas.The high vascularity of synovial membrane was essential to nourish the knee joint, and to overcome minor intracapsular trauma , tears ,destructions or diseases of knee structures. The high vascularity of synovial membrane could provide beside nourishment; cytokines and other growth factors needed to promote healing and regeneration of the injured knee. The high vascularity of synovial membrane was crucial to remove products of chondrocytes metabolism and articular matrix turnover to keep healthy joint.

The results of the present work agreed with Okuda et al, 1999 who published meniscal rasping for repair of meniscal tear in the avascular zone. They found that in rasping of parameniscal-tear, the synovium when compared to contralateral control without rasping in an animal model. Two to 4 weeks after surgery, hypertrophic synovium was observed to migrate from the parameniscal region to the tear in the rasping group. Eight to 16 weeks after surgery, the tear was almost completely healed as compared to the controls. Kobuna et al., reported a study in dogs related to the use of a synovial flap to promote healing of meniscal tears in the avascular zone. In contrast to control meniscal tears without the flap, longitudinal tears were repaired with fibrovascular tissue at 6 weeks, and the vessels extended to the white-white zone over the femoral surface of the meniscus. Healing of the meniscal lesion was thought to occur due to the vascularized synovial pedicle flap promoting neovascularization from the parameniscal area.

Krenn etal. 2006; Pessler etal. (2008); Slansky et al. (2010) reported that histological severity of synovitis of rheumatoid synovitis arthritis (RA), was high grade widespread synovitis seen in RA with synovitis abutting cartilage or meniscal lesions more than the low grade synovitis of in OA

Yves Henrotin et al. (2014) investigated the blood vessels density in N/R and I synovial biopsies using antibody against von Willebrand's factor. The analysis showed that OA blood vessels were distributed throughout the depth of the SM without preferential distribution in lining cells. Vascular density and vessels size were higher in I than in N/R biopsies. A staining for VEGF was observed in perivascular and sublining cells in both N/R and I biopsies. An acute positive staining was observed in the lining layer of I but not N/R biopsies, indicating that lining cells were key actors in the OA SM angiogenesis process.

Kennedy et al. (2010). investigated blood vessels stability in synovial tissue obtained from RA, psoriatric arthritis and OA patients using α-smooth muscle actin, a pericyte marker indicating vessel maturity .They found in sections from patients with inflammatory arthritis a mixture of immature vessels, vessels acquiring pericytes, and stable vessels, which showed close alignment of endothelial cells and pericytes. In OA tissue, all vessels had acquired pericytes and thus had undergone full maturation and stabilization. That finding explained in part the persistence of inflammation in OA synovium.

Yves Henrotin et al. (2014) had developed an original methodology which compared inflammation and angiogenesis in the SM with different grades of synovitis. They used the Ayral's macroscopic synovitis score to select, in the same OA SM, biopsies coming from N/R synovial or I areas (Lambert et al. 2012).

Synovial cells were isolated and cultured separately and the production of pro-inflammatory factors by synovial cells from N/R and I areas compared. Interestingly, cells from the I area produced more IL-6, IL-8 and VEGF, but less thrombospondin (TSP)-1 (an anti-angiogenic factor) than cells coming from the N/R area. In addition, VEGF levels were strongly correlated with IL-6 and IL-8 levels, confirming the relationship between inflammation and angiogenesis in OA. A significant negative correlation was obtained between TSP-1 and the pro-inflammatory factors IL-6 and IL-8. These results suggested a shift in the balance of angiogenic factors in favour of the development of new blood vessels. They also examined the effects of IL-1β (1 ng/ml) on the gene expression of five pro-angiogenic factors – VEGF, basic fibroblast growth factor (bFGF), NGF, angiopoietin-1 (Ang1) and MMP-2 – and three anti-angiogenic factors – vascular endothelium growth inhibitor (VEGI), TSP-1 and TSP-2. After 24 h treatment, IL-1β stimulated pro-angiogenic gene expression and strongly depressed anti-angiogenic gene expression. With regards to angiogenesis, VEGF was of outstanding importance. VEGF was probably the key regulator of neovascularization in inflammation. VEGF induced endothelial cell proliferation and migration, and also stimulated angiogenesis (Gao et al., 2013).

Yves Henrotin, et al., 2014 added that local hypoxia was a major feature of the inflammatory tissue that also triggered angiogenesis in SM. Hypoxia stimulated the expression of hypoxia inducible factor (HIF)-1α and HIF-2α which acted predominantly viaupregulation of VEGF. The direct link between accumulation of HIF-αs and overexpression of VEGF, and the important role of the VEGF angiogenic pathway in arthritis, suggested the central role of HIF-αs in the pathogenesis of OA [Giatromanolaki et al. 2003]. A significant cytoplasmic and nuclear overexpression of HIF-1α and HIF-2α was noted in the synovial lining and stromal cells of OA synovium relative to normal. Overexpression of HIF-α was related to high microvessel density, high platelet-derived endothelial cell growth factor (PD-ECGF) expression and high VEGF/kinase insert domain protein receptor (KDR) receptor activation, suggesting HIF-α dependent synovial angiogenesis in OA (Giatromanolaki et al., 2003).

Lin et al., (2012); Szekanecz and Koch (2008a, 2008b) explained that, other angiogenic mediators including hepatocyte growth factor (HGF), prostaglandins and nitric oxide (NO) were observed with hypoxia and HIFs also acted through stimulation of VEGF production during neovascularization .Interaction between VEGF and angiopoietin-1 (Ang1/Tie2) was critical for the stabilization of newly formed vessels .

Szekanecz and Koch (2008a); Szekanecz and Koch, (2001) pointed that some chemokines and chemokine receptors had been implicated in synovial inflammation and angiogenesis. Most CXC chemokines containing the glutamyl–leucyl–arginyl (ELR) amino acid sequence stimulated neovascularization while chemokines lacking that motif suppressed neovascularization. Among ELR+ chemokines, they mentioned IL-8/CXCL8 or connective tissue activating protein-III (CTAP-III/CXCL6). The most important endothelial receptor for ELR+ angiogenic CXC chemokines was represented by CXCR2.

In the present study histological examination of serial sections stained by Masson stain of parts of full term (33-36 weeks) CRL 31-34cm) of part of the synovial membrane ,in the sub intima, showed the presence of the parallel more dense collagen bundles than the previous age.. The deep sub synovial layer was formed of special organized collagen bundles of the synovial tissue that was full of numerous large branched blood vessels and fenestrated capillaries. Nissls granules of mast cells were seen disperssed near the blood vessels.

The results of the present work agreed with Phoebe R. Kreyet al., 1971who studied the Human Fetal Synovium. Histology, Fine Structure and Changes in Organ Fetal synovial tissues. They obtained postmortem Human Fetal Synovium and maintained them in organ culture. They made Preservation and morphologic differentiation, followed histologically for 2–4 weeks. They found the lining cells of the fetal synovium was found to consist of three cell types: fibroblasts, macrophages and undifferentiated cells. In culture the undifferentiated cells disappeared and the typical macrophages became scarce. Other changes observed were an apparent increase in mast cells, an intracellular accumulation of lipid inclusions, dilated endoplasmic reticulum, and intracellular collagen fibers.

Cells with (FILO) Podia and ruffled cytoplasm in the prenatal developng synovial membrane of human knee joint:

In the present study histological examination of serial sections stained by Mallory triple stain of parts of the synovial membrane of the full term fetus of the prenatal developing human knee joint showed, in the sub intima, the presence of numerous LARGE cells having podia and ruffled cytoplasm secreted substances, most probably collagen in the extra cellular matrix ECM. The LARGE cells had different shapes and size AND NUMBER OF PODIA in the deep sub intima. Another cells in the sub intima had cytoplasmic extensions similar to fibroblasts were seen. However, although advanced culture studies and in immunohistochemical studies, the workers argued if

these large (giant) cells secreting collagen were type A or B synoviocytes.

The results of the present work agreed with Barland et al. (1969) who studied the structure of the lining cells at the surface of the synovial membrane facing the joint cavity by electron microscopy. They found that the long cytoplasmic processes of those cells appeared to be oriented toward the surface of the membrane, where they overlapped and intertwined. The matrix of the lining cells contained dense material but no fibers with the periodicity of collagen. The lining cells were divided into two cell types or states of activity on the basis of their cytoplasmic contents. Type A is more numerous and contained a prominent Golgi apparatus, numerous vacuoles (0.4 to 1.5 microns in diameter) containing varying amounts of a dense granular material, many filopodia, mitochondria, intracellular fibrils, and micropinocytotic-like vesicles. Type B contains large amounts of ergastoplasm with fewer large vacuoles, micropinocytotic-like vesicles, and mitochondria. The probable functions of those cells were discussed in the light of current knowledge of the metabolism and function of the synovial membrane at that time.

Ghadially (1983); Murphy et al. (1993) who mentioned that Type A synoviocytes were macrophage-like,characterized by surface ruffles or lamellipodia (often described as filopodia,since they resembled those when sectioned, plasma membrane invagination's and associated micropinocytotic vesicles,a prominent Golgi apparatus but little granular endoplasmic reticulum.There was immunohistochemical evidence for the presence of surface receptors characteristic of macrophages on what were believed to be A synoviocytes.

In contrast, Type A synoviocytes which predominated in the intima of most species (Ghadially, 1983) resembled fibroblast, had abundant granular endoplasmic reticulum but contained fewer vacuoles and vesicles and had ruffled and branches plasma membrane than the phagocytic type. Type A synoviocytes, even when cultured, synovial fibroblasts were phenotypically distinct from ligament fibroblasts in the amount of type III collagen and hyaluronic acid produced (Murphy et al., 1993). Ghadially (1983) suggested that type A cells derived from a stem cell population in the subintima. Synoviocytes, were NOT AN actively dividing cell population in normal synovial membrane, although their division rate increased dramatically in response to acute trauma and acute heamarthrosis (Ghadially ,1983)In such conditions the type B synovial fibroblasts divided in situ, while Type A cell population increased by migration of bone marrow derived precursors. The function of the cells of the synovial intima included the removal of debris from the joint cavity mainly by type A cells and the synthesis of some of the components of the synovial fluid by both types of cells.

The results of the present work agreed with Belluzzi et al ., 2019 who mentioned that ,differently from type A synoviocytes, type B synoviocytes expressed both the surface marker CD55 and class II major histocompatibility molecules, proving a key role in early phases of immune responses in the synovial membrane. Type B synoviocytes were found further from the synovial lining; they produced mainly hyaluronic acid (one of the main components of cartilage ECM), which bonded to the cell receptor CD44. Moreover, they were active in the production of lubricin having role in articular cartilage surface-protection. The subintima outer layer showed two to three layers of synoviocytes lying over loose connective tissue rich in fibroblasts, secreting collagen, and other proteins of the ECM. It had few macrophages and lymphocytes, fat cells, and blood vessels, which were active in providing nutrients to both the synovial membrane and the cartilage tissue

Synovial fibroblasts and Undifferentiated mesenchymal cells U.D.M.C in the synovial me, mbrane of the developing prenatal human knee joint and their role in knee diseases in adult:

In the present study examination of serial sections stained by H&E and Mallory triple stain of parts of the synovial membrane of 4month fetus (13-16wks-CRL 9-14cm) and full term (33-36 weeks) CRL 31-34cm)prenatal showed the presence of fibroblasts with many cytoplasmic extensions in the intima and subintima. Undifferentiated mesenchymal cells U.D.M.C s were smaller than fibroblast were noted. The intimal matrix contained collagen.The subintima of the synovial membrane of 4month fetus stained by Mason trichrone contained areolar tissue, fat cells and numerous blood vessels.

The results of the present work agreed with Smith (2011) who mentioned that Type B synoviocytes had adapted to the production of hyaluronan.$CD86^-$ intimal fibroblasts demonstrated the high activity of the enzyme UDP Glucose dehydrogenase (UDPG) which converted UDP Glucose into UDP Glucunate, one of the two substrates required by the hyaloronan synthase for the assembly of the hyaloronan polymer. Synovial intimaL fibroblasts expressed several adhesion molecules including, vascular cell adhesion molecule, intra cellular adhesion molecule, 1VCAM1, ICAM-1, CD44.

The results of the present work agreed with The results of the present work agreed with Phoebe and Krey et al.(1971) who reported that the lining cells of the fetal synovium was found to consist of three cell types: fibroblasts, macrophages and undifferentiated

cells. In culture the undifferentiated cells disappeared and the typical macrophages became scarce.

The results of the present work agreed with Belluzzi et al ., 2019 who mentioned that The subintima outer layer showed two to three layers of synoviocytes lying over loose connective tissue rich in fibroblasts, secreting collagen, and other proteins of the ECM.. OA was often associated with synovial inflammation; that feature was mainly represented in the proximity of pathologically damaged cartilage and bone, being responsible for disease progression and symptoms (i.e., joint swelling, pain, and effusion). In addition to its involvement in early stages of the disease, synovial inflammation was also thought to be secondary to penetration of osteocartilaginous fragments and inflammatory/catabolic factors in the synovial cavity. Interestingly, all OA joint tissues were able to stimulate synoviocytes and might be involved in the progression of OA synovitis. According to the histological characterization of the tissue, the hallmarks of the synovial membrane in case of OA were hypertrophy and hyperplasia. They explained that Infrapatellar Fat Pad IFP-Synovial Membrane Mediators Involved in OA Pathology and Pain.The molecules involved in OA pain coming from IFP-synovial membrane could be divided into 3 groups: (a) neuropeptides and peptide hormones; (b) growth factors; (c) cytokines

Macrophages of the synovial membrane of the prenatal developing human knee and their role in knee diseases in adult:

In the present study histological examination of serial sections of part of the synovial membrane of 4 month fetus 13-16wks-CRL 9-14cm) and full term human (33-36 weeks) CRL 31-34cm) stained by H&E and Masson trichrome showed the presence of macrophages in the intima and subintima that increased with age progress.Few lymphocytes were also seen . The increased macrophages with age progress in the prenatal lifemight to fulfill knee joint immune needs in the developing prenatal human knee joint. Healthy joint needed elimination of intraarticular debris to reduce the effects of inflammation over time. Synovial macrophages had involvement in angiogenesis, as well as OA synovitis (Vergunst et al., 2005; De Lange-Brokaar et al., 2012). Other workers mentioned that synovial macrophages might contribute to cartilage destruction due to prolonged production of proinflammatory cytokines or through the formation of osteophytes by the release of the transforming growth factor-beta (TGF-β)3 and bone morphogenetic protein-(BMP-) 2 and BMP-4 (Belluzzi et al., 2019).

However Smith (2011) mentioned that macrophages were minority of cells in normal intima, while their numbers in inflammatory arthritis increased dramatically and in RA synovial tissue accounted for up to80%of intimal layer.More over Smith 2011 reported the presence of antigen-presenting interdigitating dendritic cells in normal synovium.

That result of the present study agreed with Rafael Iñigo Pavlovich (2008) who mentioned that synovial tissue played a key role in the immune function of the joints, and Type A synoviocytes had macrophage-like properties and carried surface antigens that were relevant to rheumatoid arthritisRA and related autoimmune disorders of joints. Synovium had immune function, phagocytosis, lubrication, and cartilage nutrition. With regard to phagocytosis, synovium could remove bacteria and` envelop small cartilage fragments that might result from joint overload, arthritis or direct trauma. Elimination of intraarticular debris reduced the deleterious effect of inflammation over time. Synovial lubrication was important to the healthy joint; synovial fluid diminished the joint frictional coefficient reducing heat and wear. Hyaluronic acid, a deformable gel that with increased elasticity as force was applied was synthesized by Type a synoviocytes, and joint forces promoted the secretion of hyaluronic acid, in part through stimulation of a Ca (21) influx-dependent activation of the PKCalpha-MEK-ERK1/2 cascade, which were extracellular signal-regulated kinases. That was functionally important because that linked joint lubrication to joint use. Moreover, chondroprotection of articulating joint surfaces was provided by lubricin, a mucinous glycoprotein that was a product of megakaryocyte-stimulating factor gene (GenBank U70136) expression; loss of synovial lubricating ability had been implicated in the pathogenesis of degenerative joint disease.

Henrotin et al. (2014) mentioned that the inflammation targeted SM (synovitis) in the early and late stages of OA. In the early stage, its distribution was confined to areas adjacent to sites of chondropathy and associated with an acceleration of cartilage degradation (chondrolysis) ([Ayral et al. 2005). that finding suggested that inflammation was brought about by cartilage breakdown. In advanced OA, synovitis had invaded across the SM, and progressed to fibrosis and villi hypertrophy (Shibakawa et al., 2003). The pathophysiological was as follows: mechanical stress directly damaged cartilage or activated chondrocytes to produce abnormal levels of matrix metalloproteinases (MMPs) and reactive oxygen species (ROS) responsible for cartilage breakdown and the release in the joint cavity of microcrystals, osteochondral fragments and products of extracellular matrix degradation. Those fragments and products triggered the secretion by cells of the inflamed synovium (synoviocytes, macrophages, lymphocytes) of cytokines, chemokines, lipidic mediators, ROS and

MMP which could directly degrade the cartilage matrix components or dysregulated chondrocyte metabolism leading to an imbalance between cartilage matrix degradation and synthesis. Cartilage breakdown products, but also pro-inflammatory mediators released by chondrocytes and other joint cells, in turn amplified the SM inflammation, creating a vicious circle. Those mediators might also trigger a systemic inflammatory response with consequent elevation of inflammatory serum biomarkers such as C-reactive protein (CRP). In OA, CRP is associated with clinical severity, the degree of inflammatory cell infiltration of the SM, disability, the number of involved joints and pain level [Stannus et al. 2013].

Yves Henrotin, et al. (2014) illustrated that OA synovium, angiogenic factors were primarily released by macrophages, endothelial cells and synoviocytes. Those factors included mainly growth factors, pro-inflammatory cytokines, chemokines, extracellular matrix protein, low oxygen tension, matrix-degrading proteolytic enzymes and cellular adhesion molecules (Szekanecz et al. 2010).

Yves Henrotin et al. (2014) explained that in OA, the SM underwent multiple structural, metabolic and functional changes that could be investigated by imaging, biochemical markers, macroscopically or microscopically. A standardized macroscopic classification based in part on SM vascularization was established by Ayral and colleagues (Ayral et al., 1996) for the arthroscopic evaluation of the SM. That scoring system distinguished three different grades: normal SM; reactive SM; and inflammatory SM. The SM in OA generally included a range of abnormalities indicative of an inflammatory synovitis such as synovial lining hyperplasia, infiltration of inflammatory cells (mainly macrophages and T lymphocytes), and an increase in vascularity and fibrosis.

Manferdini et al. (2016) held an experiment on synovial tissues that were obtained from 26 patients with OA (14 women and 12 men, mean age 66 ± 11.10 years, body mass index 28 ± 4.45 Kg/m^2, disease duration 7 ± 4.8 years) and Kellgren/Lawrence grade 3/4 [23], who were undergoing total knee replacement surgery. Subcutaneous abdominal fat was obtained from six healthy patients undergoing liposuction. The study was approved by the Rizzoli Orthopaedic Institute ethical committee and all patients provided informed consent (Protocol number 15274). They fixed the Synovial tissue specimens in B5 solution (freshly prepared 9:1 mixture of mercuric-chloride/40 % formaldehyde) at room temperature for 2 h and embedded in paraffin, and serial tissue sections (4 μm thick) from each specimen were prepared and routinely stained with hematoxylin-eosin. The histopathological features of each synovial tissue specimen were evaluated according to the synovitis inflammation scoring system described by Krenn, which rank each of the alteration evaluated (hyperplasia of the synovial lining layer, inflammatory infiltrate and stromal cell density) on a scale from 0 to 3. The parameters of synovitis inflammation scoring system were summarized as follows: 0–1 no synovitis; 2–3 low-grade synovitis; 4–6 moderate-grade synovitis; and 7–9 high-grade synovitis. The scoring was performed by two independent observers (CM and GL).

They made Immunohistochemical analysis of synovial tissue

Serial sections s incubated overnight at 4 °C with monoclonal anti-human-CD55 (2.5 μg/ml, Millipore, Temecula, CA, USA), −CD68 (10 μg/ml, Dako Cytomation, Denmark), −Factor VIII (10 μg/ml Dako), −CCL3/MIP1α (2.5 μg/ml R&D Systems, Minneapolis, MN, USA) and -S100A8 (4.5 μg/ml R&D) diluted in Tris-buffered saline (TBS) containing 0.1 % bovine serum albumin (BSA). Samples were then rinsed in TBS and sequentially incubated at room temperature for 20 minutes with multilinker biotinylated secondary antibody (Biocare Medical, Walnut Creek, CA, USA) and alkaline phosphatase-conjugated streptavidin (Biocare Medical). The reactions were developed using fast red substrate (Biocare Medical), counterstained with hematoxylin, and mounted in glycerol gel. Negative controls were performed using isotype control (Dako Cytomation). Semiquantitative analysis of immunohistochemically stained slides were performed on 20 microscopic fields (×200 magnification) for each section. The analysis was performed using Red/Green/Blue (RGB) with Software NIS-Elements and Eclipse 90i microscope (Nikon Instruments Europe BV). Briefly, they acquired the total number of blue-stained nuclei and the total number of positive-stained red cells. The data were expressed as percentage of positive cells for CD55 and CD68, respectively. For Factor VIII analysis they counted the number of positive vessels in 20 microscopic fields. The data were expressed as the mean number of positive vessels/5 mm^2 area.

Manferdini et al. (2016) mentioned that synovial macrophages were key effector cells in osteoarthritic diseases.The synovial layers in OA were composed of synovial fibroblasts (SF) and inflammatory leukocytes (lymphocytes and macrophages, SF were mesenchymal cells that displayed many characteristics of fibroblasts, including vimentin, CD55, CD90, cadherin-11, vascular adhesion molecule-1 (VCAM-1) and intracellular adhesion molecule-1 (ICAM-1).SF constitutively produced IL6, chemokine (C-X-C motif) ligand (CXCL)8/IL8, chemokine (C-C motif) ligand (CCL)2/monocyte chemotactic protein (MCP-1), transforming growth factor (TGF)β, and fibroblast growth factor.Moreover, synovium was recently

reported to contain cells that, after isolation and cell-culture expansion, displayed a mesenchymal stem cell (MSC) phenotype indistinguishable from SF . Synovial macrophage-like (SM) cells in OA showed a phenotype similar to other resident cell macrophages, including CD11b, CD14, CD16 and CD68, and they produced the main inflammatory mediators, such as IL1, IL6, TNFα, matrix metalloproteinases (MMPs) and aggrecanases (ADAMTS), which contributed to articular matrix degradation. Isolated synovial cells in OA were mainly composed of SF with 7 % SM, less than 0.5 % neutrophils and less than 0.1 % T cells. It had been shown that depletion of CD14-positive SM resulted in a decline in IL1β and TNFα, thus indicating that those cells played a role in inflammation .In the early stage of OA, a unique chemokine signature had been associated with synovial inflammation. CCL5/RANTES and CCL19/macrophage inflammatory protein (MIP)3β chemokines were mainly associated with inflammation

The results of the present study agreed with Smith (2011) who mentioned that the macrophages were found in the intima and subintimal regions of normal adult synovium. Intimal macrophages carried typical macrophages lineage markers.They showed prominent nonspecific esterase (NSE)activity and were strongly positive FegRIIIa,while subintimal macrophages usually expressed low levels of FegRIIIa or were negative .However macrophages made up minority of cells in normal intima,while the numbers in inflammatory arthritis increased dramatically and in RA synovial tissue accounted for up to80%of intimal layer.A usual pattern was that of superficial layer of macrophages with an intimal phenotype below which was a layer of intimal fibroblasts.In the subintima, there might be a zone of NSE –weak,strong CD14+fEGri+ macrophages associated with venules.There might be also small number of antigen-presenting interdigitating dendritic cells in normal synovium. Evidence todate indicated that both intimal and subintimal macrophages derived from bone marrow via circulating monocytes, might of which probably arrive via subintimsal venules and migrated to the intima.

Collagen of the synovial membrane of the prenatal developing human knee :

In the present study ,histological examination by light microscope of serial section stained with H&E,Mason trichrome and Mallory stains of parts of the synovial mem brane of 4month fetus (13-16wks-CRL 9-14cm) and full term (33-36 weeks- CRL 31-34cm) prenatal showed that in the sub sintima and deep synovium there were collagen bundles and thin elastic fibers. The collagen bundles had different thickness, length, branches and organizations . Collagen bundles increased in amount with age progress, and increased in length, thickness and differed in morphology. Some collagen bundles had special organization were seen in the deep synovium of full term. The increase in collagen and elastic fibers in the prenatal developing synovial membrane of the human knee joint with age progress might be to preparatory to the postnatal knee functions and kinematics. However, some workers accused the variety and different types of collagen in the synovial membrane of the knee joint by enhancing rheumatological diseases and enabling synovitis and synovial tissue turnover (Rafael Iñigo Pavlovich 2008)

Korochina et al. (2016) reported the change in the structural-and-functional reorganization of the collagen of the synovial membrane and articular cartilage in the knee joint in rats with experimental chronic heart failure, which indicated degeneration in the synovial and cartilage. They mentioned that separation of fibers, decrease in the relative volume density of microcirculatory vessels, and increase in the expression of MMP-9 and caspase 3 were found in the synovial membrane. A decrease in the thickness of the surface layer (tendency to erosion), vacuolization and necrosis of chondrocytes, and increase in their readiness to programmed cell death were observed in the articular cartilage. Changes in the content of type II collagen and metachromasia were revealed in the cartilage matrix. These changes illustrated the development of degenerative arthropathy in cartilage components.

Rafael Iñigo Pavlovich 2008 pointed that the nonmechanical synovial inflammation might result as a reaction to small particles of collagen type II and other cartilage derived macromolecules. That resulted in a vicious cycle where additional cartilage deterioration occurred due to the inflammatory mediators. In a study performed by Saxne et al, two groups of proteoglycan epitopes, a glycosaminoglycan-rich region of aggrecan (referred to as proteoglycan) and a hyaluronan-binding region, as well as one matrix protein, cartilage oligomeric matrix protein, were quantified by immunoassay. Synovial fluid proteoglycan concentrations were initially elevated but decreased significantly with prolonged arthritis, whereas cartilage oligomeric matrix protein levels changed less markedly and levels of hyaluronan-binding region remained stable. There was a positive correlation between synovial fluid and serum concentrations of cartilage oligomeric matrix protein in samples obtained during the early phase of the disease. That demonstrated that injury as a result of reactive, inflammatory arthritis might be temporary, as compared to rheumatoid arthritis was permanent and progressive. In addition, mononuclear cell infiltration and excessive expression of inflammatory mediators were noted in early osteoarthritis as compared to late osteoarthritis. Rafael Iñigo Pavlovich (2008) added that isolated fibroblast-like-synoviocytes were noted in different phases of

osteoarthritis. In the future those observations might have therapeutic implications for patients during the early stages of arthritis.

In the present study histological examination by light microscope of serial section stained with H&E,Mason trichrome and Mallory stains of parts of the synovial membrane of 4month fetus (13-16wks-CRL 9-14cm) and full term (33-36 weeks) CRL 31-34cm) showed that the synovial membrane was formed of intima,subintima and deep subsynovium .There was fine short collagen fibers in the intimal matrix,in the subintima and more deep synovium .The sub intima had areolar CT ,fibroblasts ,with high vascularity. Short collagen bundles were seen.

The sub intima of full term in sections stained by Mallory triple stain and Masson trichrome showed the presence of fibroblasts, macrophages,mast cells and few branched cells similar to undifferentiated mesenchyme cellsUMCs.In the subintima there were large cells having podia and ruffled cytoplasm secreted collagen,in the EXTRA cellular matrix ECM. The large thick excess bundles secreted by the giant cells occasionally masked the synoviocytes. Deeper in sub synoviun there was special organization of collagen (like feather of birds?). Excess elastic fibers were seen in deep synovial tissue of full term. The morphology of collagen differed in the matrix of the intima, subintima, and deep synoviun. Both collagen and elastic fibers stained blue by Mallory. The elastic fibers were wavy ,thin and stained yellow by Van Gieson stain ,meanwhile collagen stained brown by Van Gieson stain and were ribbon like .The presence of different types of collagen in the synovial membrane ,and elastic fibers was necessary for the optimum function of the knee joint.

The results of the present work agreed with El Rakawy (1971) and Smith (2011)

El Rakawy (1971) mentioned that a collagen fiber was actually a bundle formed of variable numbers of fibrils and the size of the fiber (bundle) depended on the number of the fibril in it. The fibers (bundles) had a wavy course. They frequently branched and united with other fibers (bundles) i.e a group of fibers might leave their own fibers (bundles)and join another. The fibers ran parallel to each other in the fibers (bundles).If a fibers (bundles) was pulled it became straight (not wavy); if the pulling was too strong the fiber broke and frayed irregularly like a rope. Collagen fibers consisted of Collagen (Collagen: glue producing). Tannic acid changed collagen to strong insoluble product .Boiling dissolved the collagenous fibers changing them to gelatin (animal glue that gel on cooling). Weak acids and alkalics made the collagenous fibers swell. Strong acids and alkalics dissolved the collagenous fibers (basis of maceration process). Van Geison stained collagenous fibers red. Mallory stained collagenous fibers blue.

El Rakawy (1971) mentioned that elastic fibers were always single and very thin. They branched and re-united frequently. Elastic fibers consisted of elastin. Elastin was very resistant it resisted boiling water,acids and alkalies.The elastic fibers in the large arteries of the Egyptian mummies was present after thousands of years from their death. There were specific stains for elastic fibers Van Geison stained elastic fibers yellow. Mallory stained elastic fibers blue. Van Geison stained collagenous fibers red and elastic fibers yellow. Mallory stain did not differentiate elastic from collagenous fibers, it stained both fibers blue.

The results of the present study agreed with Smith (2011) who mentioned that the synovial membrane was normally a thin membrane consisting of a lining and a sublining layer of cells. The lining consists of 1–3 layers of fibroblast-like synoviocytes (FLS) and macrophage-like synoviocytes (MLS) that overlayed the sublining. The lining layer was composed mainly of type III collagen, while the sublining consisted mainly of type I collagen . In normal synovium ,Intimal matrix had an amorphous or fine fibrillar structure ,contained collagen III,IV V .VI with little type I collagen, Laminin, fibronectin and chondroitin -6-sulfate–rich prpteoglcan were all found in the intimal matrix and were all components of basement membrane along with(collagenIV),but there was no basement membrane beneath the intimal layer in normal synovium.That might be due to the absence of entactin,which normally linked other components in basement membrane together. Intimal microfibrils included fibrillin-1 microfibrils, forming a basket work around cells and collagenVI microfibrils wich formed a uniform mesh.There were large amount of hyaluronan mainly in the intimal and superficial subintimal layers of normal synovium which disappeared in the deeper subintimal layer.That might indicate diffusion of hyaluronan (HA) from the surface to wards clearing lymphatics.

The mesenchyme and Undifferentiated mesenchymal cells U.D.M.C in the prenatal developing synovial membrane of human knee joint:

In the present study, histological examination of serial sections of parts of the intra articular septum of (4 month fetus 13-16wks-CRL 9-14cm) in sections stained by H&E and Mallory triple stain showed parts of the mesenchym with undifferentiated mesenchymal cells UMCs presented in two centers. . Peripheral mesenchymal tissue contained blood vessels and the next inner cartilaginous tissue was differentiated into two strata: deeply stained stratum and lightly stained stratum. Some cells showed twin appearance. That

undifferentiated areas would form the future synovial membrane and cartilaginous tissue of menisci.

The result of the prsent work agreed with Junqueira 2013t who mentioned that the fibroblast-like synoviocytes (derived from mesenchyme)

In the present study examination of serial sections stained by H&E and Mallory triple stain of parts of the developing synovial membrane of the human knee joint. of 4month fetus (13-16wks-CRL 9-14cm) and full term (33-36 weeks) CRL 31-34cm)prenatal showed the presence of fibroblasts with many cytoplasmic extensions in the intima and subintima of the synovial membrane. Undifferentiated mesenchymal cells U.D.M.C were smaller than fibroblast were noted in subintimal layer. The intimal matrix contained collagen.

The results of the present study agreed with Rafael Iñigo Pavlovich (2008) who reported that synovial cells came from the mesenchymal layer between the fourth and sixth months of embryonic development. Anatomically those could be divided in 3 layers: the intimal layer varying from 20 to 40 microns with highly oxidative cells rich in hyaluronic acid; the subintimal layer rich in vascularity as well as mucopolysaccharides; the subsynovial layer that contained an infiltrate of adipose cells embedded in conjunctive tissue. In general, 2 types of cells were found: synoviocytes Type A and Type B.Type A cells were greater in number and contained vacuoles related to phagocytic function. Type B cells had a developed ergastoplasm and were capable of transforming into fibrocytes depending on the inflammatory response to coexistent cytokines. A wide array of cytokines were produced by synovial stimulation including tumor necrosis factor, interleukin (IL)-1, IL-6, and IL-8; all played a role in the inflammatory process and tissue necrosis.

The results of the present work agreed with El Rakawy 1971 who mentioned that undifferentiated mesenchymal cells U.D.M.Cs resembled fibroblasts but were smaller, they could differentiate and produce any other type of CT cells. They were mainly present in CT of the embryo.

The results of the present work agreed with Phoebe R. Kreyet al., 1971 who pointed that Fetal synovial tissues was found to consist of three cell types: fibroblasts, macrophages and undifferentiated cells. In culture the undifferentiated cells disappeared and the typical macrophages became scarce. Other changes observed were an apparent increase in mast cells, an intracellular accumulation of lipid inclusions, dilated endoplasmic reticulum, and intracellular collagen fibers.

Sensory mechanoreceptors and free nerve endings in the prenatal developng synovial membrane of human knee joint:

In the present study histological examination by light microscope of serial sections stained with Mallory triple stain of part of L.S. of synovial membrane of the knee joint of 4 month fetus(13-16wks-CRL 9-14cm) showed that the deep subintimal layer contained Ruffini -like neuroreceptor structures with dendrite ramifications and button like endings , free nerve endings ,and Pacinian corpuscles with lamellae cell arrangement showing onion like structure were noted ,the perineural epithelium containing some blood capillaries, attached to the Pacini corpuscle were seen. The capsule of Pacinian corpuscles continued with the endoneurium of the nerve.

In the present study histological examination of sections stained by silver impregnation Gordon and Sweet, of parts of T S of the synovial membrane of the knee joint full term, showed the presence of encapsulated structures resembled Messienrs like Corpuscles with zigzaz appearance of the intra capsular nerve ending were found near the blood vessels..One axon branched and supplied two Messienrs Corpuscles like structure. Raffini Corpuscles like with button endings were noted. Pacinian corpusles with cells arranged in lamellae rappearance around a core and were found in clusters near the blood vessels were noted, and the capsule continued with the endoneurium. Pacinian corpusles had single central axon that had shed its myelin sheath at point of entery.Structure similar to Golgi tendon organ present single, elongated, oval, not near blood vessels, with large components and sensory terminals inside a capsule were noted. Free nerve endings FNE near blood vessels were ogserved. Pacinian corpusles were present more than one near blood vessels. Pacinian corpusles seemed to function in group mode when stimulated momentarily. These structures resembled the mechanoneurorecptors in the synovial membrane of the 4month fetus and full term developing prenatal human knee joint, indicated sensory functions of the prenatal human synovial membrane, and the capacity of the mechano-neuro receptor of transducing mechanical stimuli.in the prenatal human developing knee joint.

Ruffini like mechanoreceptors structure had collagenous core and several axons branched liberally were believed to contribute to muscle tone maintenance, Golgi tendon organs and Pacinian corpuscles were stimulated during knee movement, and free nerve endings were nociceptors,envolved in pain transmission and modulation of pain transmission. Thus, receptors of the prenatal developing synovial membrane of human knee joint were able to produce a discriminating afferent inflow to the central nervous system (CNS), thereby contributing to the biomechanics, kinematic ,protection ,pain transmission and modulation of pain transmission and function of the joint through the musculature.

The results of the present study were similar to Freeman and Wyke (1967) but they mentioned only four types of neuro receptors in the cat joints .They did not mention Messeners.like structure. Freeman and Wyke (1967) made anatomical and histological study in the innervation of the knee cat joint. They classified encapsulated nerve endings in the synovium as follows: Ruffini endings were low threshold, slow adapting mechanoreceptors (Type 1); Pacinian corpuscles were low threshold, rapidly adapting mechanoreceptors (Type 2); Google organs, characterized by their poor association with blood vessels, were high threshold, slowly adapting mechanoreceptors (Type 3); and free nerve endings are pain receptors (Type 4). In addition, Grönblad et al., reported substance P-immunofluorescent nerves that were closely associated with pain transmission and were found in human knee synovial membrane and menisci. Both tissues also contained enkephalin-immunofluorescent nerves, which might be involved in the modulation of pain transmission. Previous suggestions of the presence of nociceptive receptors in these non cartilaginous joint structures, made on a histological basis, were thus confirmed by immunohistochemical methods.

However, Freeman and Wyke (1967) classified 4 types of neuroreceptors in the synovial membrane of the cat joints. They did not mention Messeniers corpuscle that were noted in the present work of the developing synovial membrane of the prenatal human knee joint

The results of the present work were similar to Turlough Fitzgerald et al. (2012) who mentioned that the capsules of the free nerve endings had to be described comprised an outer coat of modified Schwann cells (telogalia). All three were mechanoreceptor transducing mechanical stimuli. They mentioned that Meissner s corpuscles lied beside the intermediate ridges of the epidermis. In these ovoid receptors, several axons zigzaz among stacks of teloglial lamellae. Meissner s corpuscles were rapidly adapting. Together with the slowly adapting Merkel cell neurite complexes, they provided the tools for delicate detective work on textured surfaces such as cloth or wood, or on embossed surfaces such as Braille text. Elevations as little as 5um in height could be detected.

Turlough Fitzgerald et al. (2012) reported that Raffini endings were found in both hairy and glabrous skin responded to drag (shearing stress) and were slowly adapting. Their structure resembled that of Golgi tendon organ having collagenous core in which several axons branched liberally. Pacinian corpuscles were the size of rice grain. They numbered about 300 in the hand. They were subcutaneous, close to the underlying periosteum numorous along the sides of the fingers and in the palm. Inside a thin connective sheath was onion like layers of perineural epithelium containing some blood capillaries .Inner most were several teloglial lamellae surrounding a single central axon that had shed its myelin sheath at point of entery. Pacinian corpuscles were rapidly adapting, and were especially responsive in vibration –particularly to bone vibration in the limbs ,many corpuscles were embedded in the periosteum.of long bones.Pacinian corpuscles discharged one or two impulses when compressed, and again when released .In the hands ,they seemed to function in group mode :when an object such as orange was picked up ,as many as 120 or more corpuscles were activated momentarily, with a momentarily repetition when the object was released. For that reason, they had been called "event detectors" during object manipulation.

The results of the present work were in accordance with Belluzzi et al. (2019) who mentioned that as demonstrated by Xu et al., the normal synovial membrane had a rich nerve supply and, including the sympathetic nervous system, most of the nerves were recognizable in proximity of the vascular networks despite not extending deep into the intimal layers.

In the present work Histological examination of sections stained by silver impregnation Gordon and Sweet, of parts of TS of the prenatal developing human synovial membrane of the knee joint of 4months fetus (13-16wks-CRL 9-14cm) and full term ,showed the presence of encapsulated structures around blood vessels,and free nerve endings that were occupying large area of the synovial tissue . At full term of the prenatal developing human knee joint stained by Gordon and sweet silver impregnation, single large oval structure resembled Golgi tendon organ ,composed of periaxial space surrounded a Capsule ,enclosing multiple inner large components,and terminals was seen. The structure that resembeled Golgi tendon organ had the largest volume among the four types of the neouroreceptors found in the present study, That indicated sensory function of the developing prenatal human synovial membrane of the knee joint.

The results of the present work were in accordance with Smith (2011) who studied the normal and mentioned that the normal synovium had a rich nerve supply including the sympathetic nervous system, most of the nerve supply was around vascular network although it did extended into the intimal layers. Consistently reduced nerve supply was seen in the synovial tissue of RA patients in the most superficial intimal region.

The result of the present work were similar to Ovalle and, Dow 1983 who compared the ultrastructure of the muscle spindle and the tendon organ of mouse and mentioned that the neruo tendenous and neurospindle consisted of outer capsule,

periaxial space surrounded the selender inner capsules, whose component cells formed attenuated branches subdividing the axial space into several components for the nuclear chain and nuclear bag intrafusal fibes and their corresponding sensory terminals (Ovalle and Dow, 1983).

Splittgerber (2019) mentioned that spindles (Golgi tendon organ) were present in tendons and were located near the junction of tendon with muscles. They provided the CNS with sensory information regarding the tension of muscles. Each spindle consisted of a fibrous capsule the sounded the small bundles of loosely arranged tendon (collagen) fibers (intrafusal fibers). The tendon.cells were larger and more numerous than those found elsewhere in the tendon.One or more myelinated sensory nerve fibers pierced the capsule ,lost their myelin sheath,branched and terminated in club-shaped endings.The nerve endings were activated by queezed by the adjacent tendon fibers within the spindle, when tension developed in the spindle tendon.Unlike the neuromuscular spindle ,which was sensitive to chages in muscle length,the neurotenenious organ detected the changes in muscle tension .

The results of the present work were similar to Wu et al. (2015) who studied and analyzed the pattern and types of sensory nerve endings in ankle collateral ligaments using histological techniques, in order to observe the morphology and distribution of mechanoreceptors in the collateral ligaments of cadaver ankle joint, and to provide the morphological evidence for the role of the ligament in joint sensory function.

Wu et al. (2015) found in the adult human ankle collateral ligaments that the Golgi tendon organs (type III) were thinly myelinated spindle-shaped corpuscles. It had the largest volume among the four types of the neouroreceptors they found in their study, with the mean size of 300 × 70 μm. The Golgi tendon organs were dyed bluish violet; with darker dyed shapelessly nerve substances. They existed singly or connected by nerve fibers. Although the Golgi tendon organs were found in all the ligaments, in their study, they were found less than Ruffini, which was not concordant with the literatures.

In the present work, histological examination of serial TS sections of parts of the synovial membrane stained with Mallory triple stain and silver impregnation-Gordon and sweet, of 4month (13-16wks-CRL 9-14cm) aged fetus and full tem showed the presence of free nerve endings around the blood vessels in the prenatal human developing synovial membrane of knee joint.

The results of the present work agreed with Zimny and Wink (199) 1who mentioned that four types of receptors had been described in the articular tissues of the knee joint in humans and animals. The first three types were encapsulated; the fourth was unencapsulated: type I, Ruffini endings; type II, Pacinian corpuscles; type III, Golgi tendon organs; and type IV, free nerve endings. Ruffini endings, Pacinian corpuscles, and free nerve endings were most prevalent in the fibrous joint capsule; Golgi tendon organs are most common in the collateral and cruciate ligaments and the menisci. In the anterior and posterior cruciate ligaments (ACL, PCL), receptors were concentrated at the tibial and femoral attachments of the ligaments. In the menisci, neural elements penetrate the horns and the outer and middle thirds of the body. Ruffini mechanoreceptors were believed to contribute mainly to maintenance of muscle tone, Pacinian corpuscles and Golgi tendon organs were stimulated during movement, and free nerve endings were nociceptors. Thus, receptors of the knee joint were able to produce a discriminating afferent inflow to the central nervous system (CNS), thereby contributing to the protection and function of the joint through the musculature.

The results of the present work simulated Wu etal. (2015) who found in the collateral ligaments of the ankle joint Free nerve endings (type IV) were non-myelinated fibers which branched from an axonal fiber . They had a diameter of 1–3 μm and were dyed lighter and lighter when got closer to the end. The amount of free nerve endings was found least in the collateral ligaments in that study.,

The developing prenatal human ligamentum patelle(anterior ligament) and the patella of 4month fetus ,and (13-16wks-CRL 9-14cm) full term human :(33-36 weeks) CRL 31-34cm)

In the present study morphological examination of the ligamentum patelle and the patella of the of 4month fetus, (13-16wks-CRL 9-14cm) showed that the patella was small cartilagenous, had no fat around it, and was attached to the ligamentum Patellæ.That cartilaginous patella represented the fore shading model of the future bony patella.

In the present study morphological examination of the ligamentum patelle of the full term human :(33-36 weeks) CRL 31- showed that, the ligamentum Patellæ was the central portion of the common tendon of the Quadriceps femoris, which was continued from the patella to the tuberosity of the tibia, the long diameter of the patella was 11mm and the transverse diameter was 9 mm. There were two areas in the inner surface of the patella :small lower part with more cartilaginous appearance and an upper part with more firm consistency and bony appearance.Infra pattellar fat pad extended around the patellar margins formed fatty ring was seen . After the ligamentum patellea was cut and reflected, two synovial thin cord plicae, which represented embryonic remnant, were seen. At adult, a big bony patella was attached to quadriceps tendon and the quadriceps tendon was sectioned and the

patellar flap retracted distally to illustrate the intra-articular structures.

The results of the present work agreed with Henry Gray 1918 who stated that the synovial membrane of the knee-joint was the largest and most extensive in the body. Commencing at the upper border of the patella, it formed a large cul-de-sac beneath the Quadriceps femoris on the lower part of the front of the femur, and frequently communicated with a bursa interposed between the tendon and the front of the femur. The pouch of synovial membrane between the Quadriceps and front of the femur was supported, during the movements of the knee, by a small muscle, the Articularis genu, which was inserted into it. On either side of the patella, the synovial membrane extended beneath the aponeuroses of the Vasti and more especially beneath that of the Vastus medialis. Below the patella it was separated from the ligamentum patellæ by a considerable quantity of fat, known as the infrapatellar pad. From the medial and lateral borders of the articular surface of the patella, reduplications of the synovial membrane projected into the interior of the joint. Those formed two fringe-like folds termed the alar folds; below, those folds converged and were continued as a single band, the patellar fold (ligamentum mucosum), to the front of the intercondyloid fossa of the femur. On either side of the joint, the synovial membrane passed downward from the femur, lining the capsule to its point of attachment to the menisci; it might then be traced over the upper surfaces of those to their free borders, and thence along their under surfaces to the tibia . At the back part of the lateral meniscus it formed a cul-de-sac between the groove on its surface and the tendon of the Popliteus; it was reflected across the front of the cruciate ligaments, which were therefore situated outside the synovial cavity.

The results of the present work agreed with Henry Gray (1821–1865) who stated that the ligamentum Patellæ (anterior ligament) was the central portion of the common tendon of the Quadriceps femoris, which was continued from the patella to the tuberosity of the tibia. It was a strong, flat, ligamentous band, about 8 cm. in length in adult, attached, above, to the apex and adjoining margins of the patella and the rough depression on its posterior surface; below, to the tuberosity of the tibia; its superficial fibers were continuous over the front of the patella with those of the tendon of the Quadriceps femoris. The medial and lateral portions of the tendon of the Quadriceps passed down on either side of the patella, to be inserted into the upper extremity of the tibia on either side of the tuberosity; those portions merged into the capsule, forming the medial and lateral patellar retinacula. The posterior surface of the ligamentum patellæ was separated from the synovial membrane of the joint by a large infrapatellar pad of fat, and from the tibia by a bursa.

In the present study histological examination by light microscope of serial sections stained by Van Gieson of TS of part of ligamentum patelle of the full term human (33-36 weeks) CRL 31-34cm): showed the presence of long thin collagen bundles interlacing regularly arranged in different directions. In Mason trichrome stain , the collagen bundles were long thin branched between fasciculi, and were interlacing with elastic fibers with curved ends regularly arranged. That collagen bundles and elastic arrangement in ligamentum patelle might be to restrict the joint movement from exaggerated movements, resist the separation of bones and to fortify the joint, meanwhile allowed a great range of movement with stretch under tension due to the presence of elastic fibers. That agreed with the QuRAAN suret al Ensan 28 as what mentioned that the Creator of the human had created the human races and fortified their structures and organs. In the present study , fortification of the knee joint were done by means of the synovial membrane,patella and ligamentum patellae ,besides the other intra and extra capsular knee joint ligaments and structures like cruciate,meniscofeoral ligaments and menisci.

The results of the present work agreed with Standring et al., 2016 mentioned that the microstructure and biology of ligaments were broadly similar to that of tendons (Rumian et al., 2007) ligaments consisted of mostly of large crimped fibers of collagen type I, and their cells were predominantly elongated fibroblasts. However there were two major differences between tendons and ligaments: one relating to gross structure, the other to composition. Structurally, ligaments tended to have fibers oriented in a range of directions because they had to resist the separation of bones in more than one direction, whereas collagen fibers in the tendon had aligned with tension in the adjacent muscle. More diverse mechanical roles of ligaments were also reflected in their composition .For example, the ligamentum flavum,which joined adjacent vertebrae in the spine,had a very high elastic content which enabled it to be stretched more than 80% when the spine was flexed, and yet remained under tension in all postures .Maintaining tension was important because that ligament lied adjacent to the spinal cord, and could impinge on it became slack and buckled when the spine was moved to extension.

The results of the present study agreed with Standring et al., (2016) who mentioned that synovial joints were freely moving joints in which the articulating bony surface were covered in smooth (hyaline) articular cartilage and separated by a film of viscous synovial fluid that served as lubricant .Joint stability was provided by a fibrous capsule (which had intrinsic ligamentous thickening) and often by internal

or external accessory ligaments. Synovial fluid which aided metabolic transport to cells in the articular cartilages was synthesized by the synovial membrane that lined the joint capsule .They pointed that forces that developed by skeletal muscles were transferred to bone by tendons and aponeurosis ,fascia ,where as ligaments prevented excessive separation of adjacent bones. All of those structures comprised dense fibrous connective tissues containing of high proportion of type I collagen.

In the present work histological examination of serial sections of part of the prenatal growing developing patella of the full term human:(33-36 weeks) CRL 31-34cm) stained with VanGaison stain, showed two areas (strata) differently stained in their extra cellular matrix ECM, with two types of tissues :cartilaginous tissue had lightly stained statum and was full of large chondrocytes with different size and few short fine collagen bundles. Some chondrocytes showed twin appearance , another stratum was firo cartilaginous tissue had deeply stained brown in the sxtracellular matix ,and contained thick long collagen bundles and fewer small chondrocytes between the collagen .The growing patella showed the interstitial growth :growth from inside in the lightly stained area, and the appositional growth from outside in the dark stratum) ;the CT pericondrium:New layers of cartilage were added from the inner condrogenic layer of the perichondrium: where undifferentiated mesenchymal cells UMC formed chondrocytes(cartilage cells).The interstitial growth: growth from inside : the single cell had a capsule, when it divided into two ,each daughter cell had its own capsule, the primary capsule disappeared and the two cells remained close to each

The different stains in the two strata of the prenatal patella of the developing human knee might be due to the different types of cells that secreted different types of extra cellular matrix ECM,in the two differently stained areas:in the types of interstiail (growth from inside)and appositional growth (growth from outside)

The results of the present work agreed with Mérida-Velasco et al. (1997) who summarized their observations of the development of the knee joint in 50 serially sectioned human embryonic and fetal lower limbs (26 embryos and 24 fetuses). They announced that epiphysis of the femur and tibia became condryfied from O'Rahilly stage 18, and ossification began during the 13th week of development. The patella appeared as a dense blastema during O'Rahilly stage 19, became condryfied during O'Rahilly stage 22, and began its ossification during the 14th week of development. The knee joint cavity appeared during O'Rahilly stage 22, initially as the femoropatellar joint.That process began at the periphery of the articular interzone.

The results of the present study agreed with El Rakawy (1971) who mentioned that in the growth of cartilage there were two methods :interstitial growth :growth from inside ,and appositional growth: growth from outside.In interstitial growth :growth from inside ,the cells in the center of a piece of cartilage could divide, the new daughter cartilage cells secreted new matrix, that made the cartilage increased in size in the same way in daugh rised when bread was made .In appositional growth (growth from outside ;the CT pericondrium:New layers of cartilage were added from the inner condrogenic layer of the perichondrium: where undifferentiated mesenchymal cells U.M.Cs formed chondrocytes (cartilage cells).Those cells secreted matrix and new cartilage was laid down under the perichondrium, thus cartilage grew.

In the present work ,histological examination of part of TS of part of the growing patella showed of full term human fetus showed the interstitial growth from inside in the lightly stained area with Van Gieson stain,and the appositional growth from outside from the CT pericondrium in the dark stratum:New layers of cartilage were added from the inner condrogenic layer of the perichondrium: where undifferentiated mesenchymal cells UMC formed chondrocytes (cartilage cells).

The results of th preset work agreed with El Rakawy 1971 who mentioned that in cartilage bone : these bones were formed in the following way:First a cartilage model of the future bone was formed in the embryo ,that cartilage model was temporary and could only support the fetus when it was young. Later when more support was needed, the cartilage model died and melted away gradually and in its place ossification occurred and bone developed. It was as if you had an old wooden house and you wanted to build in its place a new modern house: the wooden house first had to be removed. In other wards: in cartilage bones, cartilage was not transformed into bone, but was replaced by bones.

In cartilage bone ossification occurred in place of disappearing cartilage models, and the U.M.Cs came from the perichondium. In membrane bone ossification occurred in a piece of C.T. membrane and UMCs came from the C.T. membrane itself.

In growth of bones, bone could increase in size only by appositional growth(interstitial growth was impossible in bone because :1-- the matrix bone was solid that it was impossible for it to expand from inside ,and 2- the mature osteocytes were unable to divide .Any bone could increase in size by new layer of bone added to one or more of the surface.Bone growth was a surface phenomenon.The Holy Quran pointed to the appositional bone growth suert Al bakara259(the cow) [البقرة/259]{}وانظر إلى العظام كيف ننشزها as a surface phenomenon

In explanation of the meaning of (nunshezha) the Galalyin explanation of the Quraan, and in the meaning of the words of QURAAN of Asfahani and Moktar sehah: meant elevation: rising up, that meant that the Quraan had previously pointed at the only way of bone growth. How can the prophet Mohamed from 14 centuries knew that the only way for bone growth was by the surface phenomenon only: the ward :nunshezha ?the appositional growth?That previous old time,there were no mcroscopes or high technology . Suret Al Najm 3&4.That information had to be told to the prophet Mohamed from the Great Creator Allah.

[البقرة/259}وانظر إلى العظام كيف ننشزها{

In the interstitial growth: growth from inside single cell had a capsule, when it devided into two, each daughter cell had its own capsule, the primary capsule disappeared and the two cells remained close to each.

The results of the present work agreed with Sadler (2019) who mentioned that in endochondral bone formation ;mesenchymal cells began to condense and differentiate into chondrocytes,b-chondrocytes formed a cartilaginous model of the prospective bone .C&dthe center of the cartilagenous model,brought osteoblasts and restricted pro;ifirationof chondogenic cells to the ends (epiphisis)of bones.Chondrocytes towards the shaft side (diaphysis) underwent hypetrophy and apoptosis as they menerelized the surrounding matrix.Osteoblasts binded to the menireazed matrix and deposited bone matrix. Lter as blood vessels invaded the epiphesis secondary ossific centers formed. Growth of bones was maintained by proliferation of chondrocytes in the growth plate.

While the external shape was being established, mesenchyme in the buds began to condense and those cells differentiated into chondrocytes.By sixth week of development , the first hyaline models forshading the bones of the extremities were formed by those chomdrocytes and joints were formed in the cartilaginous condensations when chondrogenesis was arrested ,and joint interzone was induced. Cells in that region increased in number and density, and then a joint cavity was formed by cell death .Surrounding cells differentiated into a joint capsule .Factors regulating the positioning of the joint were not clear but the secreting molecule WNT14appeared to be the inductive signal.

Sadler (2019) also reported that ossification of the bones of the extremities ,endochondral ossification ,began by the end of the embryonic period .Primary ossification centers were present in all long bones of the limbs by the twelfth week of development. From the primary center in the shaft of diaphysis of the bone endochondral ossification gradually progressed towards he ends of the cartilaginous model.

At birth, the diaphysis of the bones was usually completely ossified, but the two ends, the epiphyses, were still cartilaginous. Shortly thereafter, however, ossification centers arouse in the epiphyses .Temporarily a cartilage plate remained between the diaphyseal and epiphyseal plate, played an important role in the growth of the bones, Endochondral ossification proceeded on both sides of the plate. When the bone had acquired its full length, the epiphyseal plate disappeared and the epiphyses united with the bone.

In long bones an epiphyseal plate was found on each extremity, in small bones as the phalanges, it was found only at one extremity and in irregular bones, such as the vertebrae, one or more primary centers of ossification and usually several secondary centers appeared.

In the preset study ,morphologic examination of the prenatal developing and adult human knee joint showed that the lateral condyle of the femur differed from the medial condyle , There was complete asymmetry of both condyles. The lower end of the medial condyle became narrower and convex with age progress.

The results of the present study agreed with Sadler 2019 who mentioned that there were many cell signaling pathways important for development, but two key pathways involved the protein SHH and the noncanonical WNT pathway,better known as PCP pathway that regulated convergent extension . SHH was almost a master gene, and when that protein product bound to its receptor patched, it removed patched inhibition in smoothened.One activated, smoothened caused upregulation of GLI Family of transcription factors that controlled downstream signals by SHH.SHH was a diffusible factor with a cholesterol molecule bound to it,and it served as morphogen by establishing concentration gradients that regulated cell responses.SHHsignaling was involved in many development events ,including stabling the midline and left-to-right asymmetry and pattering many different organs.

Conclusion:

In the present study histologic examination by light microscope of serial sections stained with H&E of part of the intra articular septum, of 4month fetus (13-16wks-CRL 9-14cm) showed part of the septum had two centers of mesenchyme that would form the future synovial membrane and cartilaginous tissue of menisci.

Histologic examination by light microscope of serial sections stained with H&E, Mason trichrome and Mallory triple stains of parts of the synovial membrane of 4month fetus (13-16wks-CRL 9-14cm) and full term (33-36 weeks) CRL 31-34cm) showed that the synovial membrane was formed of intima, subintima and deep subsynovium .There was fine thin elastic and short collagen fibers in the intimal matrix,

in the subintima increased with age progress. Deeper synovium showed areolar CT, fibroblasts, increased macrophages, high vascularity with many blood vessels and fenestrated capillaries, increased with age progress were seen. The sub intima of full term had fibroblasts, macrophages, mast cells and branched cells similar to undifferentiated mesenchyme cells (UMCS). Giant cells with podia and ruffled cytoplasm SECREETING collagen in the ECM were seen, More deeper in the sub synoviun there was special organization of collagen (like feather of birds?).Excess elastic fibers were seen in with age progress in the prenatal developing human knee joint. The morphology of collagen differed in the matrix of the intima, subintima, and deep synoviun. That might be due to the different types of collagen in the synovial membrane, and that was necessary for the optimum function of the knee joint. The intima had velli in the ages studied that increased in length,depth and decreased in the layer of cells forming the villi with age progress.Collagen,macrophages,fibroblasts, and vascularity increased in the synovial tissue with age progress in the subsynovium. Some undifferentiated mesenchymal cells were noted in the synovial membrane of the studied ages. Free nerve endings around the blood vessel, Pacini corpuscle, Raffini nerve endings with button ends were noted in 4month fetus(13-16wks-CRL 9-14cm) in the deep subintima synovial tissue stained with Mallory triple stain. Structure similar to Golgi tendon organ was noted in full term synovial issue of the prenatal human developing knee joint.

In the present study, fortification of the knee by the synovial membrane, patella and ligamentum patellae, besides the other intra and extra capsular knee joint ligaments and structures like cruciate, meniscofeoral ligaments and menisci. Coincided with Suret al ensan 28,

The presence of different types of cells, and neuro receptors,FNE, besides VARIOUS TYPES OF collagen, that were noted by histological examination by light microscope of the tiny synovial membrane SM structure of the prenatal developing human knee joint.- which was called the forgotten tissue -indicated the presence of powerful Creator Allah the most merciful the most graceful. Al thareat21.fuselat53

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مفردات ألفاظ القرآن الكريم للراغب الأصفهاني

والآية: هي العلامة الظاهرة، وحقيقته لكل شيء ظاهر، وهو ملازم لشيء لا يظهر ظهوره، فمتى أدرك مدرك الظاهر منهما علم أنه أدرك الآخر الذي لم يدركهه بذاته، إذ كان حكمهما سواء، وذلك ظاهر في المحسوسات والمعقولات، فمن علم ملازمة العلم للطريق المنهج ثم وجد العلم علم أنه وجد الطريق، وكذا إذا علم شيئا مصنوعا علم أنه لا بد له من صانع.
واشتقاق الآية إما من أي فإنها هي التي تبين أيا من أي، أو من قولهم: أوى إليه.

والصحيح أنها مشتقة من التأيي الذي هو التثبت (قال ابن منظور: يقال: قد تأييت أي: تلبثت وتحسبت) والإقامة على الشيء.
يقال: تأي، أي: ارفق (والتأيي: التنظر والتؤدة، يقال: تأيا الرجل: إذا تأنى في الأمر)، أو من قولهم: أوى إليه. وقيل للبناء العالي آية، نحو: {أتبنون بكل ريع آية تعبثون} [الشعراء/128]. ولكل جملة من القرآن دالة على حكم آية، سورة كانت أو فصولا أو فصلا من سورة، وقد يقال لكل كلام منه منفصل بفصل لفظي: آية.
وعلى هذا اعتبار آيات السور التي تعد بها السورة.
وقوله تعالى: {إن في السموات والأرض لآيات للمؤمنين} [الجاثية/3]، فهي من الآيات المعقولة التي تتفاوت بها المعرفة بحسب تفاوت منازل الناس في العلم، وكذلك قوله: {بل هو آيات بينات في صدور الذين أوتوا العلم وما يجحد بآياتنا إلا الظالمون} [العنكبوت/49]، وكذا قوله: {وكأين من آية في السموات والأرض} [يوسف/105]، وذكر في مواضع آية وفي مواضع آيات، وذلك لمعنى مخصوص (وقد بسط الكلام على ذلك الإسكافي في درة التنزيل وغرة التأويل، انظر: ص 435 - 436) ليس هذا الكتاب موضع ذكره.
وإنما قال ك {وجعلنا ابن مريم وأمه آية} [المؤمنون/50] ولم يقل: آيتين (قال ابن عرفة: ولم يقل آيتين لأن قصتهما واحدة) ؛ لأن كل واحد صار آية بالآخر. وقوله عز وجل: {وما نرسل بالآيات إلا تخويفا} [الإسراء/59] فالآيات ههنا قيل: إشارة إلى الجراد والقمل والضفادع، ونحوها من الآيات التي أرسلت إلى الأمم المتقدمة، فنبه أن ذلك إنما يفعل بمن يفعله تخويفا، وذلك أخس المنازل للمأمورين، فإن الإنسان يتحرى فعل الخير لأحد ثلاثة أشياء:
- إما أن يتحراه لرغبة أو رهبة، وهو أدنى منزلة.
- وإما أن يتحراه لطلب محمدة.
- وإما أن يتحراه للفضيلة، وهو أن يكون ذلك الشيء فاضلا في نفسه، وذلك أشرف المنازل.
فلما كانت هذه الأمة خير أمة كما قال تعالى: {كنتم خير أمة أخرجت للناس} [آل عمران/110] رفعهم عن هذه المنزلة، ونبه أنه لا يعمهم بالعذاب وإن كانت الجهلة منهم كانوا يقولون: {أمطر علينا حجارة من السماء أو ائتنا بعذاب أليم} [الأنفال/32].
وقيل: الآيات إشارة إلى الأدلة، ونبه أنه يقتصر معهم على الأدلة، ويصانون عن العذاب الذي يستعجلون به في قوله عز وجل: {يستعجلونك بالعذاب} [العنكبوت/54].
وفي بناء آية ثلاثة أقوال: قيل: هي فعلة (وهذا قول الخليل، واختاره المبرد في المقتضب 289/1)، وحق مثلها أن يكون لامه معلا دون عينه، نحو: حياة ونواة، لكن صحح لامه لوقوع الياء قبلها، نحو: راية. وقيل: هي فعلة (وهذا أصح الأقوال، وهو قول سيبويه، انظر: الكتاب 398/4؛ والمسائل الحلبيات ص 335) إلا أنها قلبت كراهة التضعيف كطائي في طيئ. وقيل هي فاعلة، وأصلها: آيية فخففت فصار آية، وذلك ضعيف لقولهم في تصغيرها: أيية، ولو كانت فاعلة لقيل: أوية (وفي هذا يقول العلامة سيدنا بن الشيخ سيدي الكبير الشنقيطي:

في آية خلف على أقوال *** ما وزنها من قبل ذا الإعلال
فقيل: أية وقيل: أيية *** وقيل: بل أيية أو أيية
كتوبة نبقة وسمره *** قصبة وذا الخليل شهرة
وعندهم أن المعل الأول *** كما هم في غاية قد جعلوا
وقيل: بل آيية كفاعلة *** وحذف العين ولا موجب له).

برأ
- أصل البرء والبراء والتبري: التقصي مما يكره مجاورته، ولذلك قيل: برأت (قال الصاغاني: وبرئت من المرض برءا، وأهل الحجاز يقولون: برأت من المرض برءا، وكلهم يقولون في المستقبل يبرأ انظر: العباب (برا)) من المرض وبرئت من فلان وتبرأت وأبرأته من كذا، وبرأته، ورجل بريء، وقوم برآء وبريئون.
قال عز وجل: {براءة من الله ورسوله} [التوبة/1]، {أن الله بريء من المشركين ورسوله} [التوبة/3]، وقال:: {أنتم بريئون مما أعمل وأنا

تعالى: {لهم البشرى في الحياة الدنيا وفي الآخرة} [يونس/64]، وقال تعالى: {لا بشرى يومئذ للمجرمين} [الفرقان/22]، {ولما جاءت رسلنا إبراهيم بالبشرى} [هود/69]، {يا بشرى هذا غلام} [يوسف/19]، {وما جعله الله إلا بشرى} [الأنفال/10].

والبشير: المبشر، قال تعالى: {فلما أن جاء البشير ألقاه على وجهه فارتد بصيرا} [يوسف/96]، {فبشر عباد} [الزمر/17]، {ومن آياته أن يرسل الرياح مبشرات} [الروم/46]، أي: تبشر بالمطر.

وقال صلى الله عليه وسلم: (انقطع الوحي ولم يبق إلا المبشرات، وهي الرؤيا الصالحة، يراها المؤمن أو ترى له) (الحديث صحيح أخرجه البخاري 331/2؛ ومسلم (479) وفيه (ذهبت النبوة وبقيت المبشرات) ؛ وأخرجه ابن ماجه 1283/1؛ وانظر: شرح السنة 204/12) وقال تعالى: {فبشره بمغفرة} [يس/11]، وقال: {فبشرهم بعذاب أليم} [آل عمران/21]، {بشر المنافقين بأن لهم} [النساء/138]، {وبشر الذين كفروا بعذاب أليم} [التوبة/3] فاستعارة ذلك تنبيه أن أسر ما يسمعونه الخبر بما ينالهم من العذاب، وذلك نحو قول الشاعر:

- 54 - تحية بينهم ضرب وجيع

(هذا عجز بيت لعمرو بن معد يكرب، وصدره:

وخيل قد دلفت لها بخيل

وهو في البصائر 201/2؛ وخزانة الأدب 252/9؛ وديوانه ص 149؛ والممتع ص 260؛ والخصائص 368/1)

ويصح أن يكون على ذلك قوله تعالى: {قل: تمتعوا فإن مصيركم إلى النار} [إبراهيم/30]، وقال عز وجل: {وإذا بشر أحدهم بما ضرب للرحمن مثلا ظل وجهه مسودا وهو كظيم} [الزخرف/17].

ويقال: أبشر، أي: وجد بشارة، نحو: أبقل وأمحل، {وأبشروا بالجنة التي كنتم توعدون} [فصلت/30]، وأبشرت الأرض: حسن طلوع نبتها، ومنه قول ابن مسعود رضي الله عنه: (من أحب القرآن فليبشر) (أخرجه ابن أبي شيبة 133/6 وانظره: في الغريبين 180/1؛ واللسان (بشر) ؛ والنهاية 129/1) أي: فليسر. قال الفراء إذا ثقل فمن البشرى، وإذا خففت فمن السرور يقال: بشرته فبشر، نحو: جبرته فجبر، وقال سيبويه (الكتاب 235/2) : فأبشر، قال ابن قتيبة (في غريب الحديث 234/2) : هو من بشرت الأديم، إذا رققت وجهه، قال: ومعناه فليضمر نفسه، كما روي: (إن وراءنا عقبة لا يقطعها إلا الضمر من الرجال) (راجع: اللسان (بشر) 60/4. الحديث أخرجه ابن مردويه والطبراني عن أبي الدرداء سمعت رسول الله صلى الله عليه وسلم يقول: (إن أمامكم عقبة كؤدا لا يجوزها المثقلون، فأنا أريد أتخفف لتلك العقبة) وإسناده صحيح. راجع: الدر المنثور 523/8؛ والرغيب والترهيب 85/4. وأسباب ورود الحديث 42/2 وأخرجه البزار بلفظ: (إن بين أيديكم عقبة)، وعلى الأول قول الشاعر:

- 55 - فأعنهم وابشر بما بشروا به *** وإذا هم نزلوا بضنك فانزل (البيت لعبد قيس بن خفاف وهو شاعر جاهلي كان يعاصر حاتم طيئ.

والبيت في المفضليات ص 384؛ والأصمعيات ص 230؛ واللسان (بشر)، وتهذيب إصلاح المنطق 89/1؛ ومعاني الفراء 212/1)

وتباشير الوجه وبشره: ما يبدو من سروره، وتباشير الصبح: ما يبدو من أوائله.

وتباشير النخيل: ما يبدو من رطبه، ويسمى ما يعطي المبشر: بشرى وبشارة.

فصل

- الفصل: إبانة أحد الشيئين من الآخر: حتى يكون بينهما فرجة، ومنه قيل المفاصل، الواحد مفصل، وفصلت الشاة: قطعت مفاصلها، وفصل القوم عن مكان كذا، وانفصلوا: فارقوه. قال تعالى: {ولما فصلت العير قال أبوهم} [يوسف/94]، ويستعمل ذلك في الأفعال والأقوال نحو قوله: {إن يوم الفصل ميقاتهم أجمعين} [الدخان/40]، {هذا يوم الفصل} [الصافات/21]، أي: اليوم يبين الحق من الباطل، ويفصل بين الناس بالحكم، وعلى ذلك قوله: {يفصل بينهم} [الحج/17]، {وهو خير الفاصلين} [الأنعام/57]. وفصل الخطاب: ما فيه قطع الحكم، وحكم بريء مما تعملون} [يونس/41]، {إنا برآء منكم ومما تعبدون من دون الله} [الممتحنة/4]، {وإذ قال إبراهيم لأبيه وقومه إنني براء مما تعبدون} [الزخرف/26]، {فبرأه الله مما قالوا} [الأحزاب/69]، وقال: {إذ تبرأ الذين اتبعوا من الذين اتبعوا} [البقرة/166].

والبارئ خص بوصف الله تعالى، نحو قوله: {الباريء المصور} [الحشر/24]، وقوله تعالى: {فتوبوا إلى بارئكم} [البقرة/54]، والبرية: الخلق، قيل: أصله الهمز فترك (انظر: المجمل 122/1؛ والعباب (برأ 52/1؛ واللسان (برأ))، وقيل: بل ذلك من قولهم: بريت العود، وسميت برية لكونها مبرية من البرى (انظر: اللسان (برأ) 31/1) أي: التراب، بدلالة قوله تعالى: {خلقكم من تراب} [غافر/67]، وقوله تعالى: {أولئك هم خير البرية} [البينة/7]، وقال: {شر البرية} [البينة/6].

بشر

- البشرة: ظاهر الجلد، والأدمة: باطنه، كذا قال عامة الأدباء، وقال أبو زيد بعكس ذلك (ذكر قوله الأزهري في تهذيبه 360/11، والذي غلطه ثعلب)، وغلطه أبو العباس وغيره، وجمعها: بشر وأبشار، وعبر عن الإنسان بالبشر اعتبارا بظهور جلده من الشعر، بخلاف الحيوانات التي عليها الصوف أو الشعر أو الوبر، واستوى في لفظ البشر الواحد والجمع، وثني فقال تعالى: {أنؤمن لبشرين} [المؤمنون/47].

وخص في القرآن كل موضع اعتبر من الإنسان جثته وظاهره بلفظ البشر، نحو: {الذي خلق من الماء بشرا} [الفرقان/54]، وقال عز وجل: {إني خالق بشرا من طين} [ص/71]، ولما أراد الكفار الغض من الأنبياء اعتبروا ذلك فقالوا: {إن هذا إلا قول البشر} [المدثر/25]، وقال تعالى: {أبشرا منا واحدا نتبعه} [القمر/24]، {ما أنتم إلا بشر مثلنا} [يس/15]، {أنؤمن لبشرين مثلنا} [المؤمنون/47]، {قالوا أبشر يهدونا} [التغابن/6]، وعلى هذا قال: {إنما بشر مثلكم} [الكهف/110]، تنبيها أن الناس يتساوون في البشرية، وإنما يتفاضلون بما يختصون به من المعارف الجليلة والأعمال الجميلة، ولذلك قال بعده: {يوحي إلى} [الكهف/110]، تنبيها أني بذلك تميزت عنكم. وقال تعالى: {لم يمسسني بشر} [مريم/20] فخص لفظ البشر، وقوله: {فتمثل لها بشرا سويا} [مريم/17] فعبارة عن الملائكة، ونبه انه تشبح لها وتراءى لها بصورة بشر، وقوله تعالى: {ما هذا بشرا} [يوسف/31] فإعظام له وإجلال وأنه أشرف وأكرم من أن يكون جوهره البشر.

وبشرت الأديم: أصبت بشرته، نحو: أنفته ورجلته، ومنه: بشر الجراد الأرض إذا أكلته، والمباشرة: الإفضاء بالبشرتين، وكني بها عن الجماع في قوله: {ولا تباشروهن وأنتم عاكفون في المساجد} [البقرة/187]، وقال تعالى: {فالآن باشروهن} [البقرة/187].

وفلان مؤدم مبشر (قال ابن منظور: وفي الصحاح: فلان مؤدم مبشر: إذا كان كاملا من الرجال)، أصله من قولهم: أبشره الله وآدمه، أي: جعل له بشرة وأدمة محمودة، ثم عبر بذلك عن الكامل الذي يجمع بين الفضيلتين الظاهرة والباطنة.

وقيل معناه: جمع لين الأدمة وخشونة البشرة، وأبشرت الرجل وبشرته وبشرته: أخبرته بسار بسط بشرة وجهه، وذلك أن النفس إذا سرت انتشر الدم فيها انتشار الماء في الشجر، وبين هذه الألفاظ فروق، فإن بشرته عام، وأبشرته نحو: أحمدته، وبشرته على التكثير، وأبشر يكون لازما ومتعديا، يقال: بشرته فأبشر، أي: استبشر، وأبشرته، وقرئ: {يبشرك} [آل عمران/39] و {يبشرك} (وهي قراءة حمزة والكسائي بفتح الياء وإسكان الباء وضم الشين) و (يبشرك) (وهي قراءة شاذة؛ وانظر الحجة للقراء السبعة 42/3) قال الله عز وجل: {لا توجل إنا نبشرك بغلام عليم قال: أبشرتموني على أن منسي الكبر فيم تبشرون قالوا: بشرنا بالحق} [الحجر/53 - 54].

واستبشر: إذا وجد ما يبشره من الفرح، قال تعالى: {ويستبشرون بالذين لم يلحقوا بهم من خلفهم} [آل عمران/170]، {يستبشرون بنعمة من الله وفضل} [آل عمران/171]، وقال تعالى: {وجاء أهل المدينة يستبشرون} [الحج/67]. ويقال للخبر السار: البشارة والبشرى، قال

chemicals for the histological study, and allowing collecting the miscarriages.

NB: Worth Mention: To Whom It May Concern:

All the papers published by nasra ayoub, about musk and basil(ocimum basilcum) were stolen from prof manal g abd elwahab,the papers were stolen, by Nasra Ayoub,Soad Hanem, Fergani,Mansi ,Alaa El Deen ,as the work about aromatherapy by musk and basil were published in the magazines of Ejaz, Muslim world League THE year 1433 HIJI number 40 pp 11&41pp34 and on the cover of the magazine In addition,Prof Manal . produced and discussed five written projects in English about MUSK AND BASIL aromatherapy in front of the scientific committee of the chair of applied Prophetic Medicine at King Fahd center, KING Abdul-Aziz university-Jedda -KSA, in the presence of ,Prof MOSSA Shaker.Soad jaoni, ,Prof Sawsan Rohayem THE Prof of the chair ,and 40 international scientists and the signature of the attendance ,besides the secretory of the chair Rasha.Nasra Ayoub stole one single research about musk -The first serial papers of musk and Badi. .Nasra Ayoub stole 8 shared papers, and attributed the work to her self first name. Soad Stole 7 papers. The work of musk and basil was after reaches for 10 years by Prof Manal. Nasra atrebuted only one paper about musk to Manal and another 4 papers only.Nasra and Soad attributed two papers to themselves and 4 other thieves, whom had nothing to do with the project, although the project and the the applied experiment was one belonged to Manal Nasra cheated and signed the name of Manal on the contract of King Abd Aziz University with out the knowledge of Prof Manal. Soad Jaoni, Abd Gawad SAWI, and shiek Abullah Musleh took the thieves NASRA and Soad Shaker to present the stolen papers, To Dubie conference, the year 2019. Soad Jaon, the survisor of the chair of the prophetic medicine ,Abd Gawad Sawi, shiek Musleh had kwon that the papers were stolen ,in spite of that, they took the thieves and supported them to present the stolen papers.Only the good straight person was Prof dr Korayem who was the director of the research unit in the university and chief editor of Ejaz magazine had terminated the presence of Nasra and Soad Shaker from the research unit in the university after their non-honest work and steeling of the work of Prof dr, Manal about musk and basil

Author contribution"

- Role of Manal G. Abdelwahab- :Knee Dissection, collecting specimens ,staining slides, photographing , writing and revising the paper.
- Role of-Sohair A. Sadek: collecting the miscarriages.
- Role of Sarah Mohamed Mustafa Marzouk presented this paper in year 2017 at the fifth

Acknowledgement:

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فيصل، ولسان مفصل. قال: {وكل شيء فصلناه تفصيلا} [الإسراء/12]، {ألر كتاب أحكمت آياته ثم فصلت من لدن حكيم خبير} [هود/1]، إشارة إلى ما قال: {تبيانا لكل شيء وهدى ورحمة} [النحل/ 89]. وفصيلة الرجل: عشيرته المنفصلة عنه، قال: {وفصيلته التي تؤويه} [المعارج/13]، والفصال: التفريق بين الصبي والرضاع، قال: {فإن أراد فصالا عن تراض منهما} [البقرة/233]، {وفصاله في عامين} [لقمان/14]، ومنه: الفصيل، لكن اختص بالحوار، والمفصل من القرآن، السبع الأخير (المفصل في القرآن من الحجرات إلى الناس، وقيل غير ذلك. انظر: البصائر 194/4)، وذلك للفصل بين القصص بالسور القصار، والفواصل: آواخر الآي، وفواصل القلادة: شذر يفصل به بينها، وقيل: الفصيل: حائط دون سور المدينة (انظر: المجمل 722/3؛ والبصائر 194/4)، وفي الحديث: (من أنفق نفقة فاصلة فله من الأجر كذا) (الحديث عن أبي عبيدة قال: سمعت رسول الله صلى الله عليه وسلم يقول: (من أنفق نفقة فاصلة في سبيل الله فبسبعمائة، ومن أنفق على نفسه وأهله وعاد مريضا أو ماز أذى فالحسنة بعشر أمثالها والصوم جنة ما لم يخرقها، ومن ابتلاه في جسده فهو له حطة) أخرجه أحمد 195/1، قال الهيثمي: وفيه بشار بن أبي سيف ولم أر من وثقه ولا جرحه، وبقية رجاله ثقات. مجمع الزوائد 303/2. قلت: وله طريق آخر عند أحمد. أنظر: المسند 196/1، وقال ابن حجر: بشار بن أبي سيف مقبول. انظر: تقريب التهذيب ص 122) أي: نفقة تفصل بين الكفر والإيمان.

مختار الصحاح شبكة مشكاة الإسلامية

* أ ن س * * الإنس * البشر والواحد * إنسي * بالكسر وسكون النون و * أنسي * بفتحتين والجمع * أناسي * قال الله تعالى { وأناسي كثيرا { وكذا * الأناسية * مثل الصيارفة والصياقلة ويقال للمرأة أيضا * إنسان * ولا يقال أنسانة وإنسان العين المثال الذي يرى في السوادوجمعه * أناسي * أيضا وتصغير إنسان * أنيسان * قال بن عباس رضي الله عنه إنما سمي إنسانا لأنه عهد إليه فنسي و * الأناس * بالضم لغة في * االناس * وهو الأصل و * الأنيس * المؤانس وكل ما يؤنس به وما بالدار * أنيس * أي أحد و * آنسه * بالمد أبصره و * آنس * منه رشدا أيضا علمه وآنس الصوت أيضا سمعه و * الإيناس * خلاف الإيحاش وكذا * التأنيس * وكانت العرب تسمي يوم الخميس * مؤنسا * و * يونس * بضم النون وفتحها وكسرها اسم رجل وحكي فيه الهمز أيضا و * الأنس * بفتحتين لغة في الإنس والأنس أيضا ضد الوحشة وهو مصدر * أنس * به من باب طرب و * انسة * أيضا بفتحتين وفيه لغة أخرى * أنس * به يأنس بالكسر * أنسا * بالضم

* ف ص ل * * الفصل * واحد * الفصول * و * فصل * الشيء * فانفصل * أي قطعه فانقطع وبابه ضرب و * فصل * من الناحية خرج وبابه جلس وفصل الرضيع عن أمه يفصله بالكسر * فصالا * و * افتصله * أي فطمه و * فاصل * شريكه و * المفصل * بوزن المجلس واحد * مفاصل * الأعضاء و * المفصل * بوزن المبضع اللسان وفي الحديث { من أنفق نفقة فاصلة فله من الأجر كذا { فتفسيره أنها التي فصلت بين ايمانه وكفره و * الفصيل * ولد الناقة إذا فصل عن أمه والجمع * فصلان * و * فصال * و * فصيلة * الرجل رهطه الادنون يقال جاءوا بفصيلتهم أي بأجمعهم وعقد * مفصل * أي جعل بين كل لؤلؤتين خرزة و * التفصيل * أيضا التبيين و * فصل * القصاب الشاة تفصيلا * أي عضاها و * الفيصل * الحاكم وقيل الفضاء بين الحق والباطل

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