AGE-RELATED CHANGES WITHIN THE KNEE

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The development of cartilage damage in synovial joints is a characteristic feature of osteoarthritis, but very similar changes are seen in ageing joints unaffected by disease. Thus, before any attempt can be made to understand the pathogenesis of osteoarthritis, it is important to have a clear understanding of the effects of ageing on the condition of a synovial joint. In an attempt to clearly define the changes seen with ageing alone, knee joints of individuals with no known history of joint disease were examined and the pattern of cartilage damage was mapped macroscopically in a manner that allowed quantitation of the affected areas.

A number of factors have been proposed to play a role in the development of cartilage damage in osteoarthritis; these include changes in subchondral vascularity, in the thickness of the zone of calcified cartilage, and changes in the structure of the subchondral bone plate and of the cancellous bony network. In order to determine whether any of these changes could account for either the cartilage damage seen with increasing age, or for regional differences in cartilage damage, blocks taken from the patella, trochlea, medial femoral condyle and medial tibial plateau were examined histologically and quantitated using image analysis techniques. The parameters examined included total cartilage, calcified cartilage and subchondral plate thickness, subchondral vascularity and the structure of the cancellous bony network. Macroscopic techniques were used to determine the distribution of trabecular microfractures and subchondral vessels within the knee.

These factors were then related to overlying cartilage condition, to age and to regional differences in cartilage condition in an attempt to determine which factors best explained the observed pattern and nature of age-related cartilage

condition within the knee. The conclusion of the study is that although subchondral vascularity appears related to cartilage condition, the factor that best explains the pattern and distribution of cartilage damage within the knee is the structure and density of the subchondral bone.

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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ACKNOWLEDGEMENTS

CHAPTER 1 : INTRODUCTION

1.1 Introduction

Cartilage loss and degeneration are characteristic features of osteoarthritis, a degenerative disease of synovial joints such as the knee. Radiological surveys reveal 4.9% of all women and 2.6% of all men have changes consistent with osteoarthritis [26] and this increases to 44% of people over the age of 80 [37]. Joints affected by this disease develop cartilage fibrillation, bone exposure and growths of new osteoarticular material [37,131]. In the early stages it may be hard to differentiate such diseased joints from those showing the degenerative changes associated simply with ageing [59,63]. Subclinical macroscopic cartilage changes are frequently seen in the knee at autopsy and in people younger than those typically affected by osteoarthritis [59]. The factors that may initiate or promote such changes are poorly understood. Although mechanical factors, typically the impulsive loading forces passing through the knee with weight-bearing, are undoubtedly involved [113], the manner and site in which these forces act remains unclear. In order to determine possible factors involved in age-related cartilage degeneration in the knee, it is first necessary to understand the forces and structures involved, as well as the possible mechanisms of cartilage damage.

1.2 Anatomy and function of the knee

The knee is a highly mobile and frequently injured weight-bearing joint that is made up of two articular compartments, the tibiofemoral and the patellofemoral joints (Figure 1.1). The tibial plateau is divided into two articular facets, the lateral facet curving more extensively posteriorly than the medial facet [70] (Figure 1.2). The femoral condyles are quite disparate in shape, the medial condyle being longer, narrower and more curved than the lateral condyle [70] (Figure 1.3). The opposing surfaces of the tibiofemoral joint appear incongruous, but this allows the wide range of flexion possible in the knee. Lying between the tibial and femoral articulating
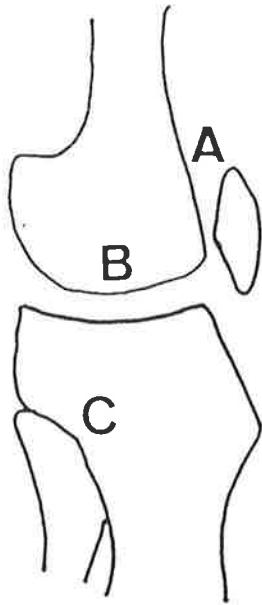
Figure 1.1 : Medial view of the knee

A - Patellofemoral joint
B - Tibiofemoral joint
C - Tibiofibular joint
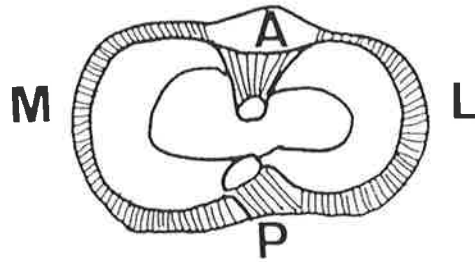
Figure 1.2 : Articular surface of the tibia showing the extent of the menisci and the attachments of the cruciate ligaments.

A - Anterior   P - Posterior
L - Lateral   M - Medial
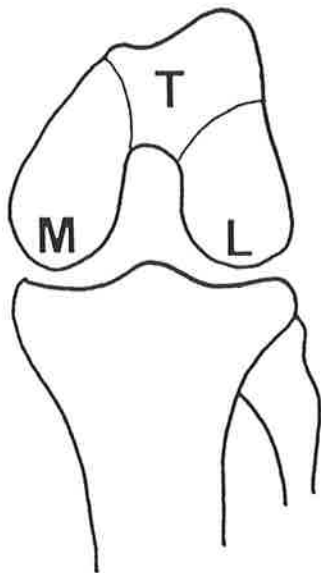
Figure 1.3 :   Anterior view of the knee

T - Trochlea
M - Medial condyle
L - Lateral condyle
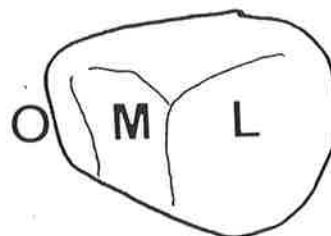
Figure 1.4 :   Articular surface of the patella

M - Medial facet
L - Lateral facet
O - Odd facet

surfaces are the semilunar cartilages or menisci. The medial meniscus can be differentiated from the lateral meniscus by the fact that its shape is less circular and that it covers a smaller proportion of the articular surface [123]. Both menisci are attached to the tibial plateau at their extremities (Figure 1.2), but the lateral meniscus is less constrained in its movement than the medial meniscus which is attached posteriorly to the tibia and the joint capsule [40,70,124]. The menisci have been shown to have a major role in load bearing across the tibiofemoral joint [62,66,74,124,126,143] carrying approximately 45% of the load [66,126]. Surgical removal of the menisci is associated with a high frequency of joint degeneration [60].

The patella articulates with the trochlea or trochlear groove of the femur. Its articular surface is divided by a central vertical ridge into a lateral and medial facet, and the latter may include a more medial, so called odd facet [45,70] (Figure 1.4). The patella is connected by the quadriceps tendon to the muscles of the anterior thigh and to the tibial tubercle by the ligamentum patellae [70].

The movements of the knee range from 0 degrees in full extension, to 150 to 160 degrees in full flexion [70]. The knee also exhibits a limited range of active internal and external rotation, but this is not possible when the knee is flexed beyond 90 degrees because of the surrounding soft tissues [100]. Flexion of the knee and active rotation are the result of contraction of the hamstrings, and extension is achieved by the action of the quadriceps femoris [70].

As the knee reaches the limits of extension, because of the disparity in femoral condylar size, there is a simultaneous, passive external rotation of the femur on the tibia, the so-called 'screw-home' movement, which provides greater stability to the knee than if it were a simple hinge joint [100]. In extension the superior part of the patella is not in contact with the trochlea at all but with the subsynovial fat pad [45,148]. As the knee flexes the patella moves down and by 90 degrees of flexion, the entire articular surface of the patella lies over the trochlea. As the knee flexes further, the patella drops between the femoral condyles [45,148]

and articulates with the inner aspect of the medial condyle [45]. Also during flexion, the tibiofemoral contact areas move posteriorly [74,144] and become smaller [62].

The knee is widely used in daily life and the loading on the knee may reach 3.03 times body weight at the moment of heel strike during normal walking [95].

1.3 Patterns of cartilage damage with ageing

In a study published in 1933 [63] cartilage 'erosions' were found in the knees of 63.5% of people at autopsy. These lesions were more frequent with increasing age, and ranged in size from 2 millimetres to 4 centimetres in diameter, and in severity from simple roughening of the surface to bone exposure. Such erosions were often multiple and opposing surfaces were frequently affected. The patella was most frequently involved, followed by the trochlea, the femoral condyles, and the tibial plateaux. Erosions were noted to be more extensive in the elderly.

Similar observations were made in a later study of 100 knee joints obtained at autopsy, with 81% of patellae showing some cartilage changes [61]. It was noted that whilst the medial femoral condyles were more frequently fibrillated than the lateral condyles, the opposite was true in the case of the tibial plateaux.

In more recent studies, the pattern of evolution of age-related changes in the knee has been determined. The patellofemoral joint is the first compartment to be affected. By the second decade of life, areas of fibrillation can be seen [7,32], and these areas progress to involve first the medial facet and then the lateral facet of the patella [2,47]. Changes likely to progress to bone exposure, however, are more frequently seen on the lateral or mid-line regions [32]. After the age of 50, full thickness cartilage loss has been found in the patella in 40% of a normal population [32,84] with the area of the medial facet affected remaining greater than that of the lateral facet [4,61]. In the tibiofemoral joint, degeneration is first seen in the second decade, full thickness loss is not seen except in the knees of people over the age of

80 [83], and the medial compartment is worst affected at all ages [4]. The degeneration of the tibial joint surface is influenced by the presence of the meniscal cartilages. Those areas which are not covered by the menisci are more likely to become softened and fibrillated, the affected area increasing with age [83], while those areas of the tibial articular cartilage underlying the menisci tend to remain intact until a much later age [4,15,83]. The exception to this is the frequent development of cartilage damage in discrete areas beneath the posterior aspect of the lateral meniscus [15,83].

1.4 Structure of a synovial joint

All synovial joints are made up of similar elements. Articular or hyaline cartilage acting as a bearing surface, lies on a layer of calcified cartilage attached to the subchondral bone plate which merges with the cancellous and cortical elements of the epiphysis of the bone (Figure 1.5).

1.4.1 Hyaline cartilage

Cartilage is made up of cells, chondrocytes, that are surrounded by a matrix consisting of collagen, proteoglycans and water [38]. Proteoglycans consist of a protein core and 50 to 100 linked glycosaminoglycans [38]. The collagen network provides tensile strength [38] whilst the proteoglycans form aggregates with water and link proteins which contribute to cartilage elasticity so that cartilage is able to absorb some of the potentially destructive loading forces that pass through a joint. [147]. In immature cartilage the proteoglycan component consists of chondroitin-4-sulphate and chondroitin-6-sulphate in equal amounts, but, with ageing, the proportion of chondroitin-6-sulphate increases as does the amount of keratan sulphate [147] and there is a decrease in the large, glycosaminoglycan-rich proteoglycans [119]. The aggregates formed by the proteoglycans are present maximally at birth, decrease during development, and reach a plateau at maturity [26]. In histological sections, the distribution of proteoglycans within the matrix
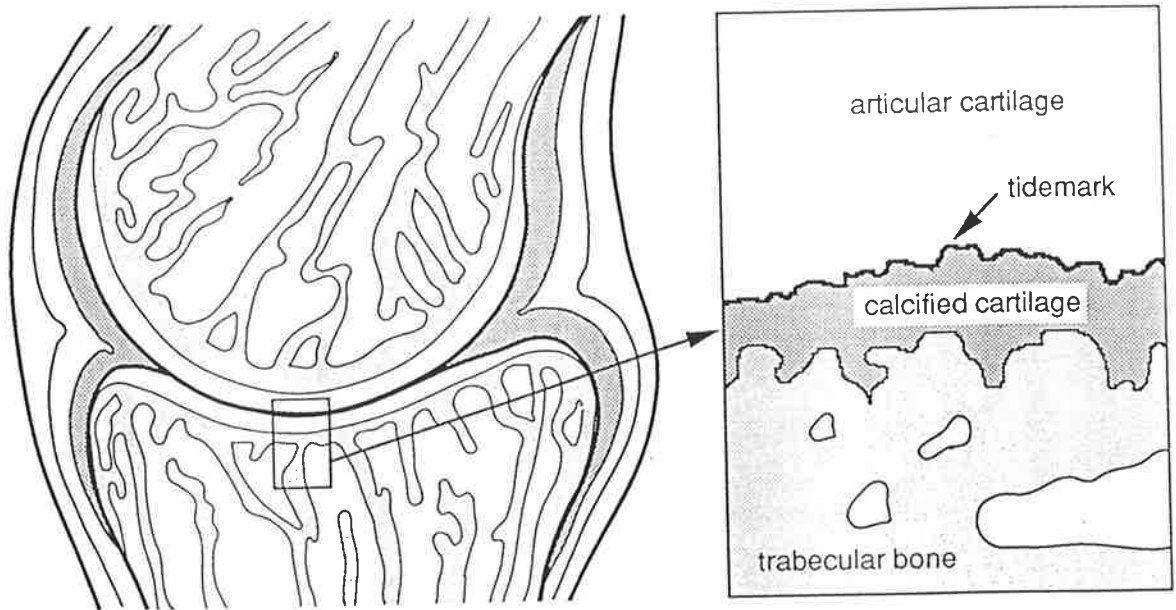
Figure 1.5 :   Schematic representation of the bone
-cartilage interface in a synovial joint.

may be assessed using proteoglycan specific dyes such as Safranin O or Alcian Blue [93,121].

There is a decrease in cartilage cellularity throughout the period of development and maturation, but, between the ages of 30 to 80 years, there is no significant change in the cell density of the full thickness of cartilage [80,87,133]. Cellular activity, as measured by the uptake of radioactively labelled sulphate, shows no change with age and may be quite high in the elderly [76]. The arrangement of the collagen network also appears unchanged with age [38].

Cartilage damage commences as a slight increase in the degree of irregularity of the cartilage surface seen only by electron microscopy, but, with time, this irregularity may progress to cartilage fibrillation [132]. Light microscopy shows damage progressing from surface irregularity to clefting (Figures 1.6 and 1.7) which goes deeper into the cartilage until there is complete disorganisation of the structure (Figures 1.8 and 1.9). Associated with clefting is an increasingly severe degree of ground substance loss, evidenced by the use of proteoglycan-specific stains, and initial hypercellularity and cloning are eventually followed by hypocellularity [73].

The pattern of age-related changes in many joints is such that loading alone is unable to explain cartilage damage : the periphery, the non-loaded area, is often the site of earliest change, as seen in the patellofemoral joint [90], the shoulder [89], the hip [89], the ankle [90] and the elbow [47]. Cartilage in loaded areas of the joint tends to be thicker [31,64,98] and contains more proteoglycan [64,136,140,152], in contrast to the proteoglycan deficiency typically seen in damaged cartilage [73]. *In vitro* work, where high density chondrocyte cultures exposed to intermittent compressive forces increased their production of proteoglycan [140], suggests that cartilage can positively respond to loading and that some degree of loading is necessary to maintain cartilage integrity: there is a loss of staining of proteoglycans and a decrease in cartilage thickness in unloaded joints in experimental animals [138]. In the normal state, cartilage damage only occasionally

Figure 1.6 : Photomicrograph of intact cartilage from the left tibia of an 18 year old female. Stained with Alcian Blue and a counter stain of Acid fuchsin and eosin. Magnification x 110 .

Note the intact cartilage surface and the dark staining of the cartilage matrix.

Figure 1.7 : Photomicrograph of cartilage showing early stages of fibrillation with clefting. Specimen from the right patella of a 77 year old female. Stained with Alcian Blue and a counter stain of Acid fuchsin and eosin. Magnification x 110 .

Note the irregularity of the cartilage surface and the loss of Alcian Blue staining from the upper zones of the hyalinee cartilage.
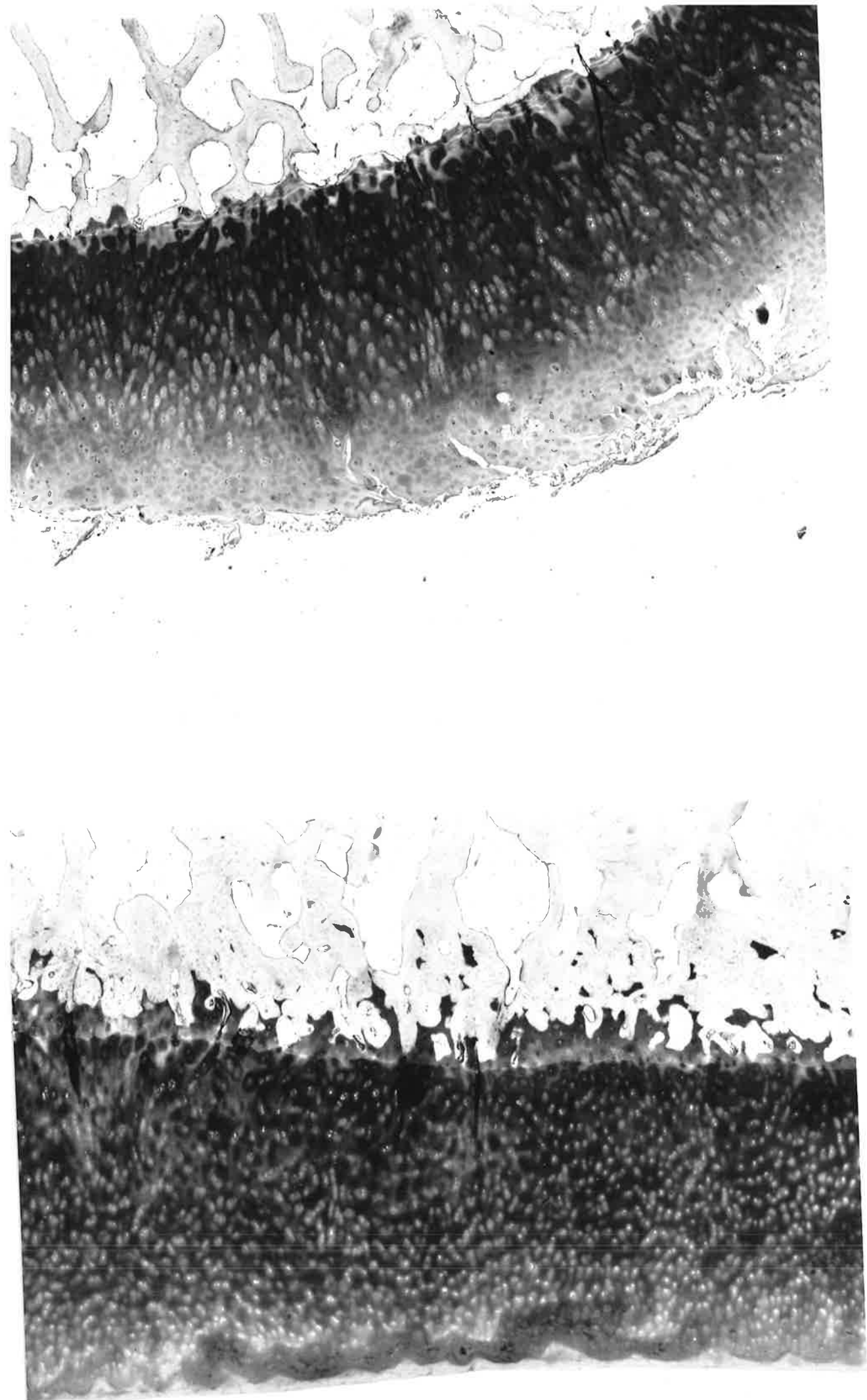
Figure 1.8 : Photomicrograph of cartilage showing late stages of fibrillation with deeper clefting and loss of staining of hyaline cartilage matrix. Specimen from the left patella of a 63 year old male. Stained with Alcian Blue and a counter stain of Acid fuchsin and eosin. Magnification x 110 .

Figure 1.9 : Photomicrograph of cartilage showing complete loss of hyaline cartilage and exposure of the underlying bone. Specimen from the left patella of a 78 year old female. Stained with Alcian Blue and a counter stain of Acid fuchsin and eosin. Magnification x 110 .
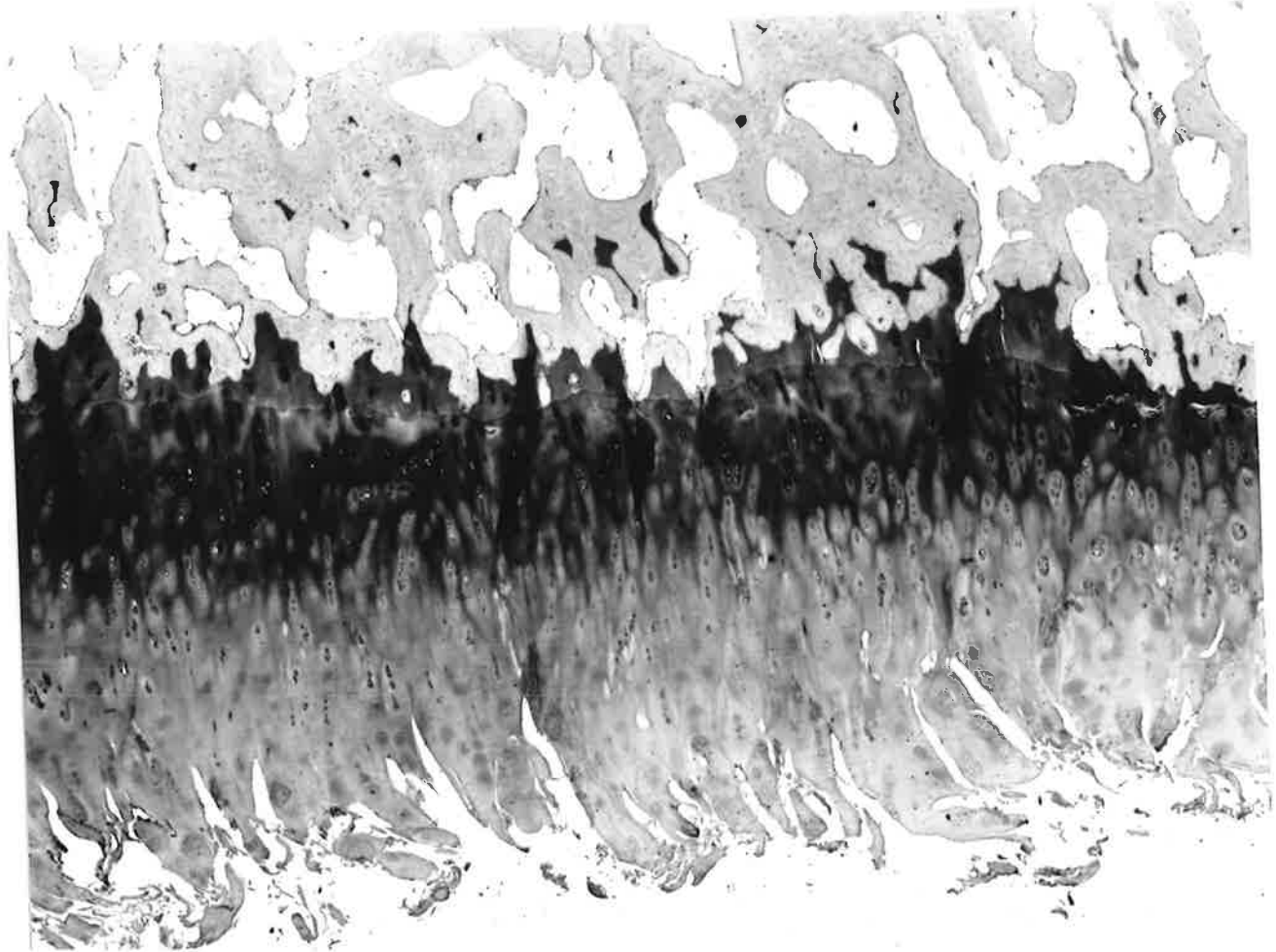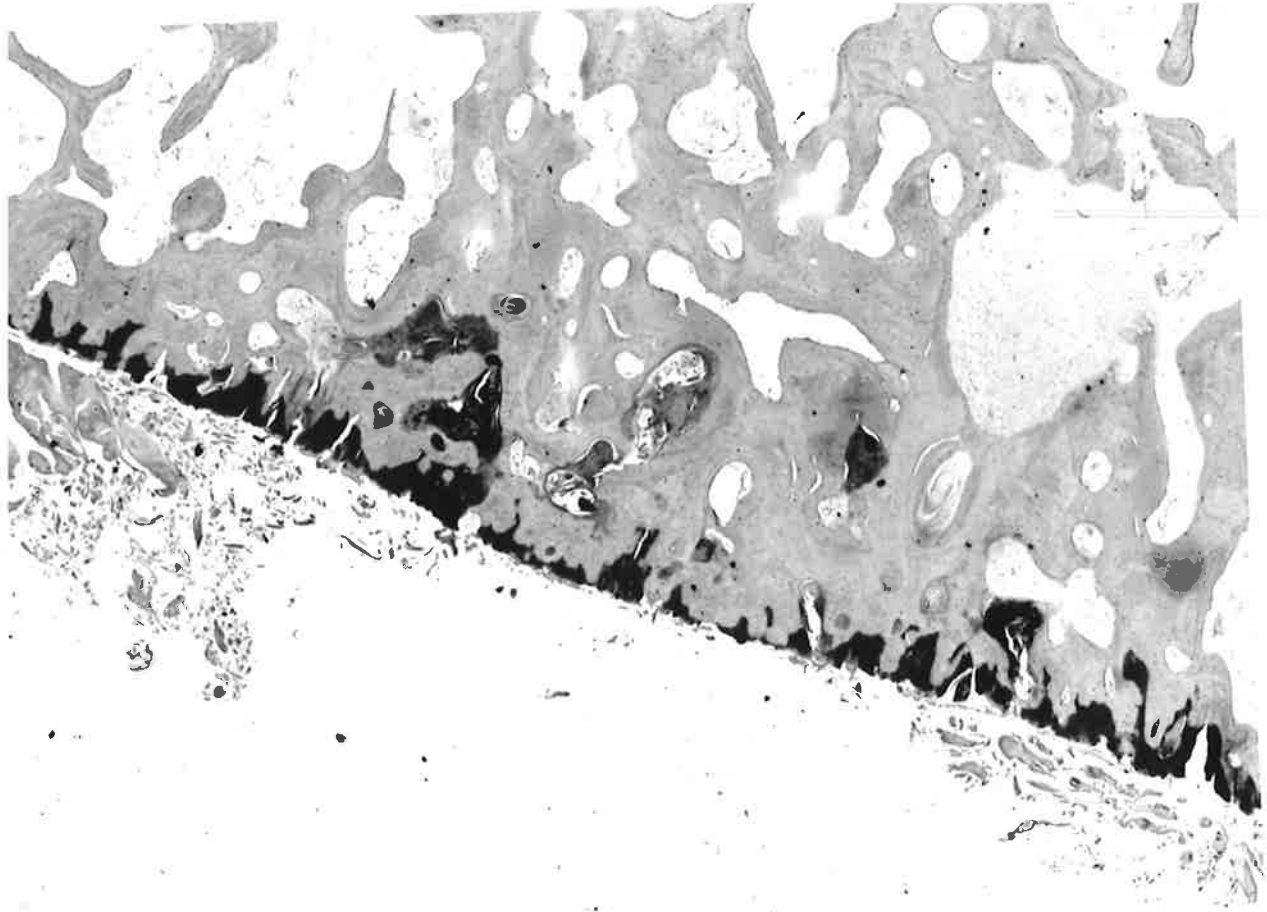
progresses to full thickness loss [78,89], as can be confirmed experimentally. Contusion or scarification of articular cartilage in animals is not associated with progressive cartilage damage [79,112]. Byers et al [16] have divided cartilage degeneration in the hip into non-progressive changes, frequent in non-weight-bearing areas, which rarely lead to bone exposure and do not interfere with function, and progressive changes, typical of weight-bearing areas within the hip, which are less frequent and develop later in life.

Cartilage damage leads to attempts at repair. Areas of degenerate cartilage are associated with the development of cell clusters, known as chondrones, and an increase in cell activity, as measured by the incorporation of radioactive sulphate into newly synthesized proteoglycan [23,24,79]. There also exists a direct correlation between the severity of cartilage damage and proteoglycan loss, and the rate of DNA and polysaccharide synthesis [23]. There is, however, a specific point at which the reparative mechanism fails and degeneration continues unabated [73]. Thus, chondrocytes are unable at any time to repair articular cartilage to structural normality [23], and, at best, the end result is fibrocartilage formation [91].

1.4.2 Calcified cartilage and the tidemark

The zone of calcified cartilage is delineated by the so-called 'tidemark' above and by the osteochondral junction below, although occasional islands of calcified cartilage may be seen deep in the subchondral bone [136]. Calcified cartilage appears to be derived from the progressive mineralisation of hyaline cartilage, and the tidemark is also known as the mineralisation front [49]. The tidemark is usually single in younger people (Figure 1.10) but becomes multiple with increasing age [7,48,68] (Figure 1.11) : this has been considered evidence of episodes of reactivation of the calcification front that occur intermittently throughout life [85]. Duplication is also associated with fibrillation of the cartilage surface, although the duplication commonly extends more widely than the area of fibrillation [48]. The tidemark is characterised by a concentration of lipids and

Figure 1.10 : Photomicrograph of the bone-cartilage interface showing a single dark staining tidemark. Specimen from the left femur of a 64 year old female. Stained with Alcian Blue and a counter stain of Acid fuchsin and eosin. Magnification x 660 .

Figure 1.11 : Photomicrograph of the bone-cartilage interface showing multiple tidemarks. Specimen from the right patella of a 77 year old female. Stained with Alcian Blue and a counter stain of Acid fuchsin and eosin. Magnification x 660 .
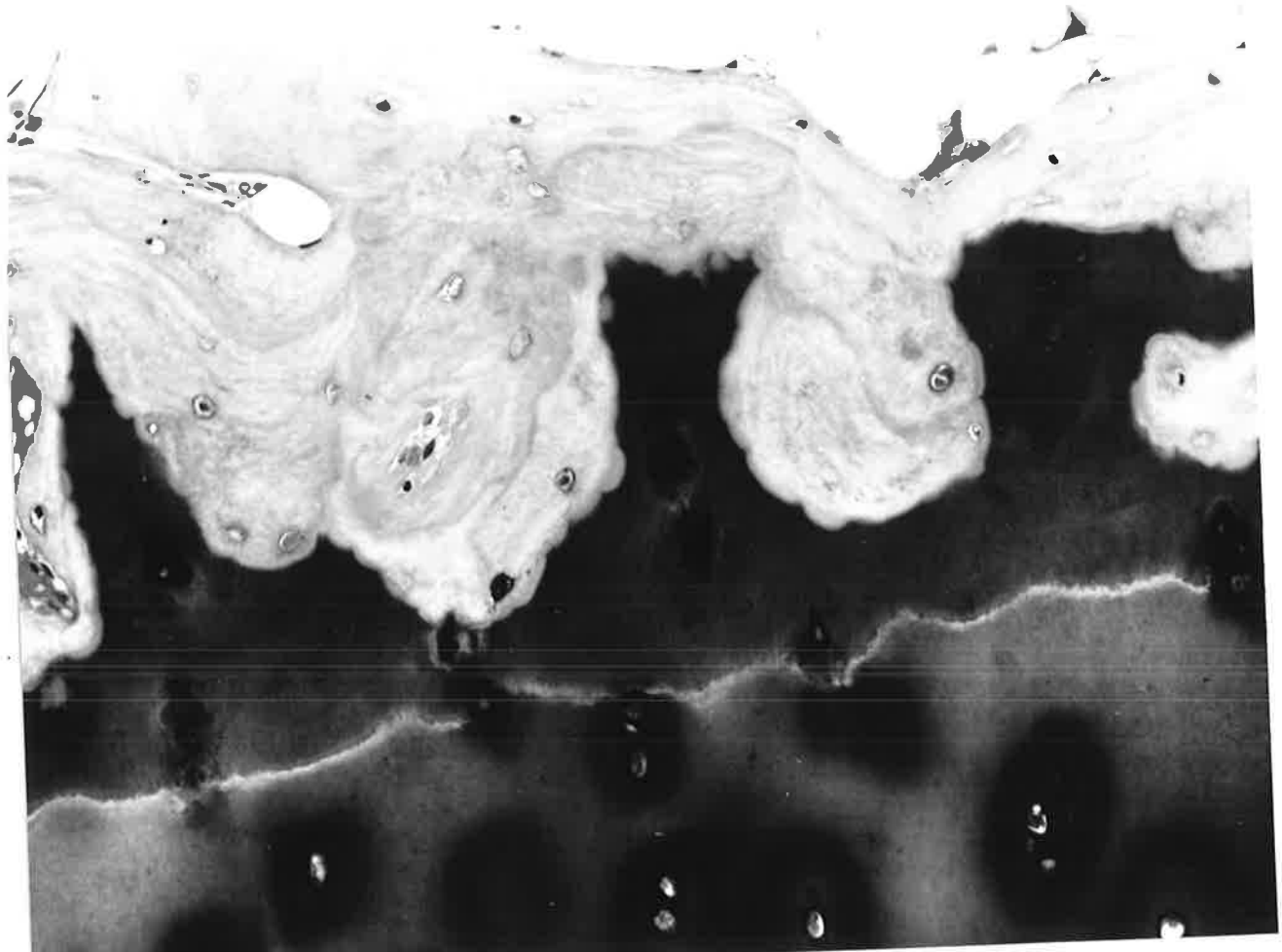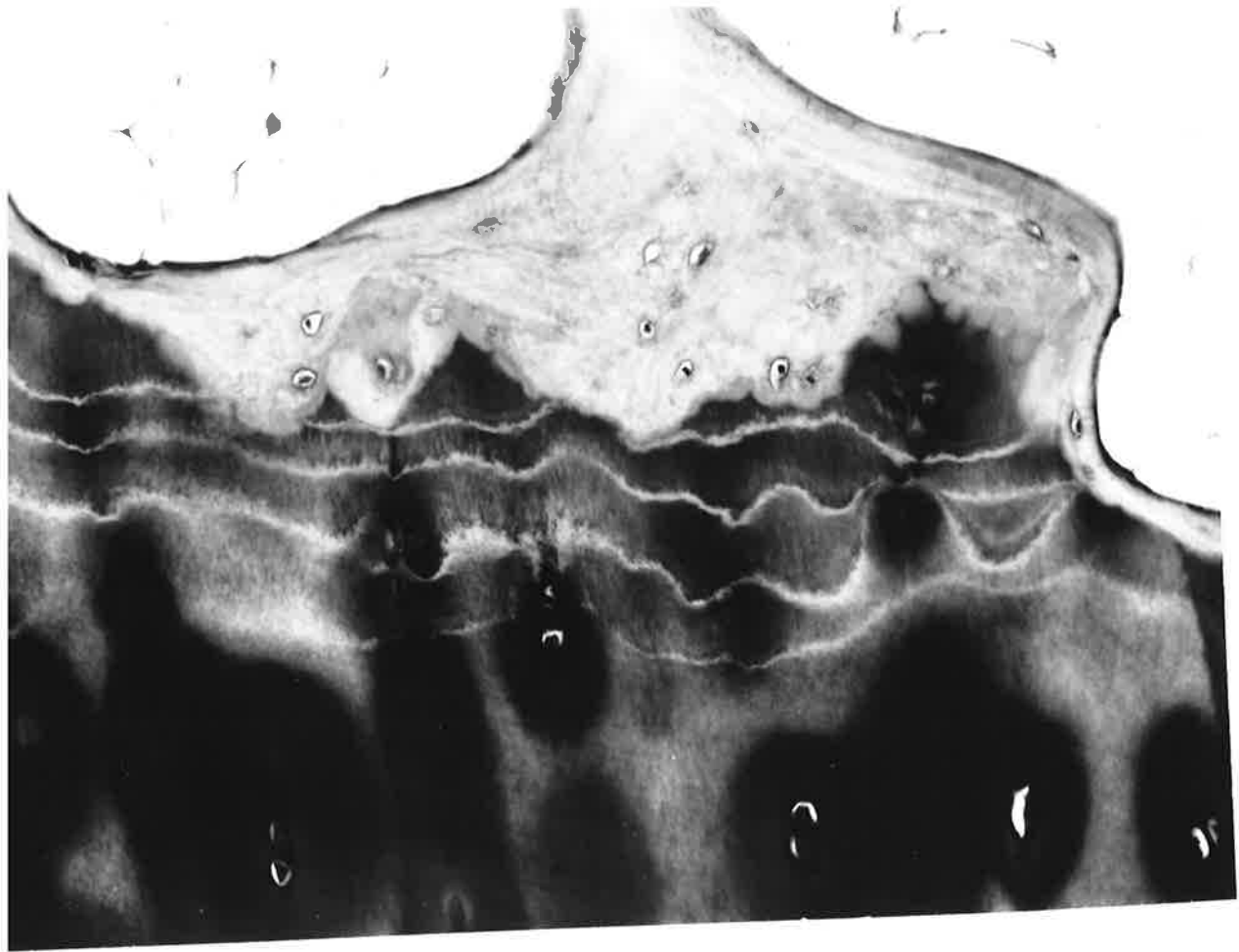
alkaline phosphatase and a paucity of proteoglycan, and is similar in composition to the epiphyseal growth plate [68]. Type X collagen, believed to provide a matrix for calcification during bone formation in the growth plate, has also been found in the calcified cartilage of dogs, where it is localised around chondrocytes just at or above the tidemark [42]. Electron microscopy has shown chondrocytes trapped in the tidemark and surrounded by calcium, as well as the presence of the extra-cellular vesicles associated with hydroxyapatite formation, lying along collagen fibres at the tidemark [14]. These observations support the hypothesis of the tidemark acting as a centre of calcification of hyaline cartilage. Positive tetracycline labelling, indicating active mineralisation, has been seen in the tidemark of a number of experimental animals, indicating episodes of mineralisation which appear to be intermittent and which do not necessarily occur throughout a joint at any one time [71]. Positive labelling of the tidemark and calcified cartilage was found in over 50% of patients undergoing total hip replacement [117]. In nearly all cases with double tidemarks, both tidemarks were labelled and the distance between the two labels was much greater than that between the double labels in bone. This indicates that either both tidemarks were active at the same time, or that there is a very high appositional rate in calcified cartilage. The nature of the factors which activate and control the tidemark remain unknown.

Apart from being involved in calcification, it has been suggested that the tidemark has a role as an anchoring network of collagen fibres, attaching articular cartilage to bone and providing a transitional zone between calcified and noncalcified tissues [116]. The variable morphology of the tidemark has been explained in terms of biomechanics, with the well aligned, densely packed collagen fibres which form a smooth tidemark being adaptations to high compressive stresses [12], whereas an irregular, undulating tidemark is best suited to resisting shear forces acting on a joint [12,116].

The thickness of calcified cartilage ranges from 20 to 230 microns [48,97], and although the amount of calcified cartilage as a proportion of total cartilage

remains constant within a single bone, the thickness varies significantly between individuals [97]. It is not clear what influence age has on calcified cartilage thickness: one study determined that age had no effect [48], while another found calcified cartilage thickness to decrease with increasing age [68]. Within the femoral head, calcified cartilage appears to be thicker in the inferomedial area as opposed to the zenith, but this difference disappears if the calcified cartilage between any multiple tidemarks is included in the calculation [85]. The role of the calcified zone appears to be the bonding of bone and cartilage, providing a zone of transitional stiffness [48,68]. Collagen fibres course freely across the tidemark without interruption [56], but there is no direct connection across the osteochondral junction. No collagen fibres can be seen crossing the osteochondral junction even by electron microscopy [12,21,56], although collagen fibres have been seen coming up from both calcified cartilage and bone and interdigitating [56]. The junction itself is approximately 600 to 1900 nanometres wide, a relatively electron lucent zone occupied largely by collagen fibres unlike those either in bone or cartilage [56]. Some strength appears to derive from the interdigitation of the calcified zone with the irregular projections of the subchondral bone plate [13], an arrangement which also acts to convert shear stresses into compressive forces on the bone-cartilage interface [108]. The junction appears to be thinner and more irregular in specimens from younger people [56], but does not appear to differ between stressed and non-stressed areas of a joint [135].

1.4.3. Subchondral bone

The bone in synovial joints consists of a subchondral plate, continuous with the shafts of the long bone and the underlying network of cancellous bone. The volume of bone is known to decrease with age and this appears to be by the loss of trabeculae from the structure [92]. A possible role for bone in the development of cartilage damage was first suggested by Radin et al [111,112]. Studying the attenuation of dynamic peak forces in synovial joints in vitro, they concluded that

although cartilage was far more compliant than bone, the cancellous network probably contributed equally to the attenuation of potentially damaging impulse forces because it was present in considerably greater volume. Thus, increases in bone stiffness alter the absorption of impulse loading forces that may potentially damage the articular surface [107]. A number of studies show that bone underlying cartilage showing the earliest histochemical signs of damage, is significantly stiffer than bone underlying essentially normal cartilage [105,114,115]. Also, although cartilage damage may be seen on both the medial and lateral aspects of the patella, it is more likely to progress to bone exposure on the lateral aspect which lies over denser, stiffer bone [104], and damage may be initiated by shear forces acting on the cartilage which lies over areas where the subchondral bone undergoes sudden changes of density [2].

It has been proposed that bone may become stiffer by the mechanism of trabecular microfracture, callus formation and remodelling, leading to thicker, less compliant trabeculae [114]. Pugh et al [106] found, when studying the medial tibia, that there was a constant relationship between the stiffness of bone and the numbers of healing trabecular microfractures. Experiments where rabbits were exposed to intermittent loading found that there was an increase in bone stiffness and in trabecular microfractures when compared to controls [106]. Dinley [27] found there were increased numbers of trabecular microfractures in osteoarthritic femoral heads, but a number of other studies have found trabecular microfracture numbers to be decreased in osteoarthritis [17,36,65]. Alternatively, as suggested by Pugh et al [105], bone stiffness may be increased by changes in trabecular architecture such as an increase in trabecular contiguity.

1.4.4 Subchondral vascularity

A recent study of osteoarthritic knees has suggested that the sclerosis of the subchondral plate, often present in this condition, may affect cartilage by decreasing the nutrition provided to the deeper layers of cartilage by subchondral vessels [29].

Although articular cartilage has long been considered an avascular structure, and the bone-cartilage interface to be impermeable in the mature joint [55,75], a number of researchers have described the presence of vascular connections between the medullary cavity and the deeper layers of cartilage. Amongst the first to do so were Holmdahl and Ingelmark [54], who described two forms of these so-called focal contacts, ampulla-like and dendritic. Further study found focal contacts to range from 15 to 50 microns in width, and to take up 1-7% of the articular surface in rabbits [59]. Focal contacts have been found in man in the ankle [10], the hip [69,153], the knee [28,29] and the temperomandibular joint [145], and have been used to explain the passage of various substances, including fluorescein dye [9], starch particles [59], radioactively labelled sulphate [53] and radioactive gold [59], from the marrow cavity to the joint space. In 1970, Woods et al [153] reclassified focal contacts as being either vascular, consisting of a vessel surrounded by soft tissue or woven bone, or non-vascular where the vessel appeared to be completely bone invested (Figures 1.12 and 1.13). They also examined the femoral head and determined that focal contacts were more numerous where cartilage was thicker and the load was presumed to be greater [153]. The vascular nature of these contacts has been confirmed on electron microscopy [94] and by a number of histological studies [69,85,83]. The study by Lane et al [69] determined that values obtained histologically parallelled those obtained by counting the number of vessels visible on the surface of the femoral head viewed en face through a dissecting microscope after the cartilage had been removed.

The fact that there is a decrease in the numbers of focal contacts with increasing age [85,153] suggests that the loss of nutrition subsequent to the loss of blood supply to the deeper layers of cartilage may explain the development of age-related changes. Lane et al [69], however, found a slight but definite increase in the numbers of focal contacts after the age of 70, and linked this to an increase in bone remodelling in the subchondral region. A number of researchers have always considered the role of focal contacts to be in the remodelling of subchondral bone

Figure 1.12 : Photomicrograph of the calcified cartilage layer showing a vascular focal contact passing from the marrow space to the deeper layers of cartilage. Specimen from the right patella of an 81 year old male. Stained with Alcian Blue and a counter stain of Acid fuchsin and eosin. Magnification x 660 .

Figure 1.13 : Photomicrograph showing focal contacts with various amounts of bone enveloping them . Specimen from the right femur of a 22 year old male. Stained with Alcian Blue and a counter stain of Acid fuchsin and eosin.
Magnification x 660 .
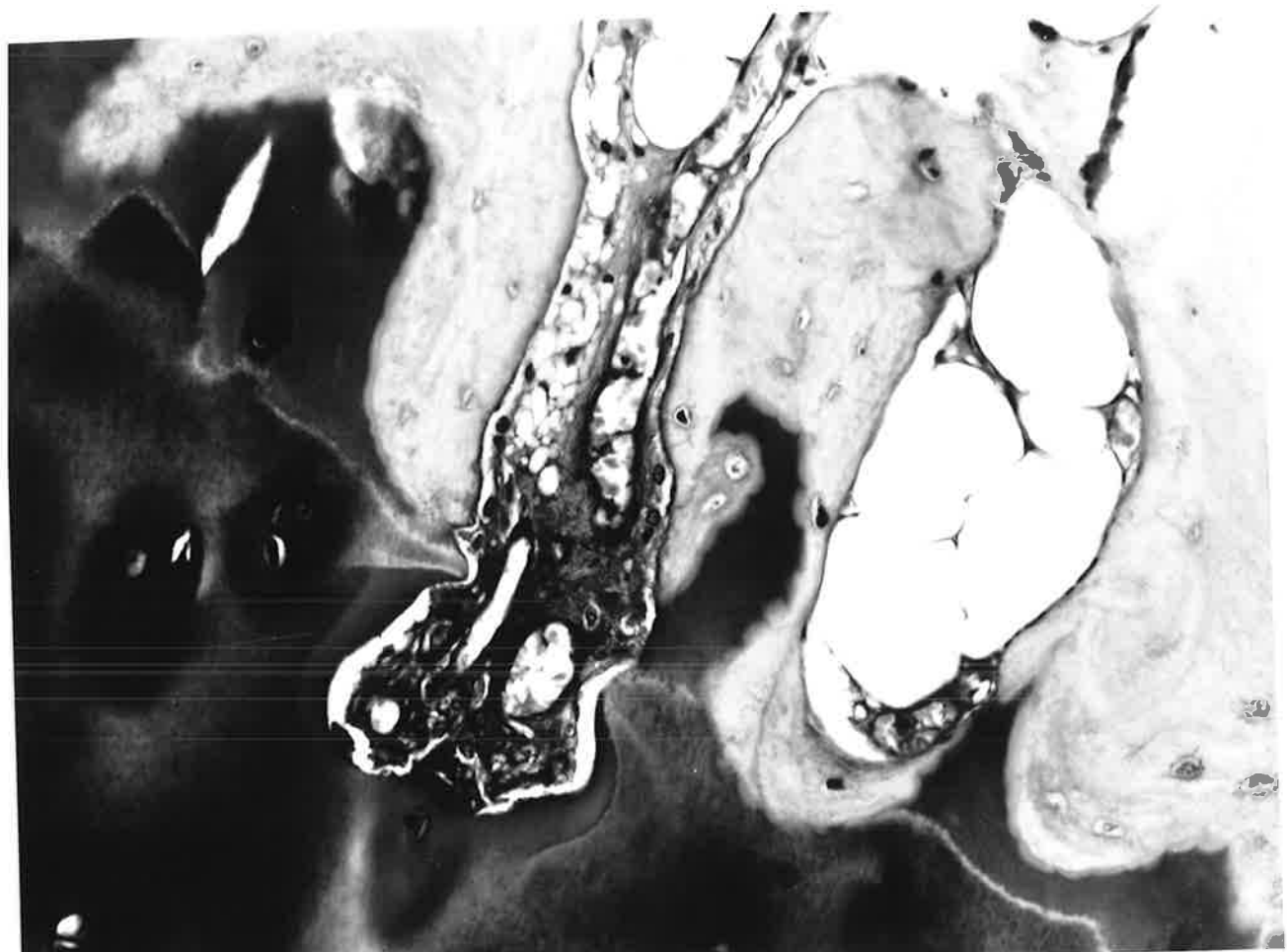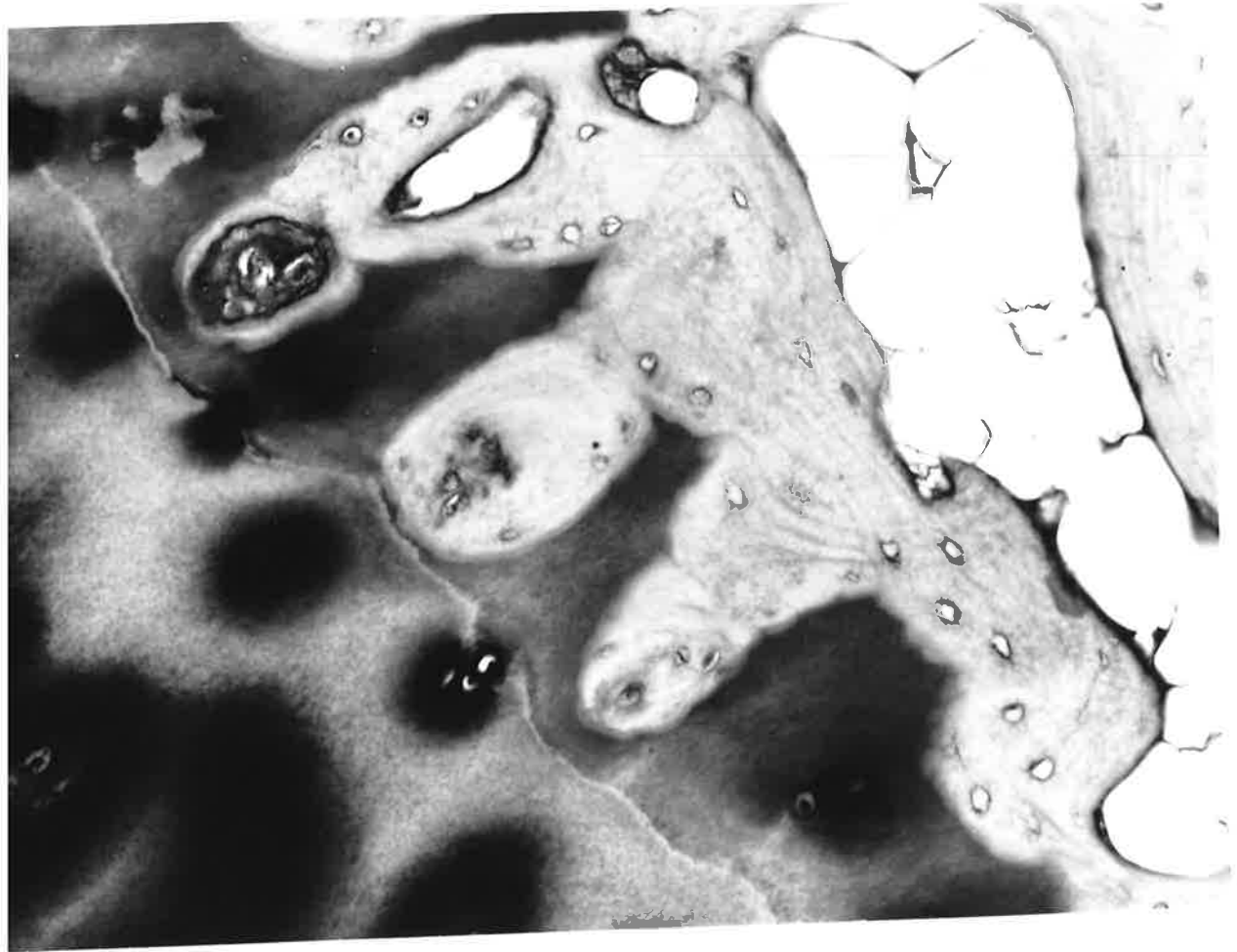
rather than in the nutrition of cartilage [25,43,49,77,145]. It is proposed that, as in the case of cartilage canals *in utero*, the vessels precede calcification [43] : calcified cartilage is remodelled by focal contacts and is replaced by lamellar bone to form part of the subchondral plate [49]. Woods et al [153] proposed that the various forms of focal contact they had described represented different phases in this process, with the soft tissue vascular contact representing the stage of cartilage resorption, followed by the initial laying down of woven bone around the vessel, and the final envelopment of the vessel by bone. Recent experimental work in mice using polychrome labelling has found new bone formation does occur around subchondral vessels [8] and repeated loading of joints in rabbits has been found to result in an increase in vascularity and bone mass [33]. Subchondral bone remodelling and replacement of calcified cartilage by bone will lead to limited long bone growth after epiphyseal fusion, which in turn may result in dysplastic joint remodelling and possibly osteoarthritis [109]. It remains unclear what stimulates vessel encroachment on cartilage: some believe that cartilage is a focus for vascular invasion throughout development [19], whilst others consider that uncalcified cartilage is protected by an anti-invasion factor in the form of 1,000 - 50,000 MW protein fraction [67], and that this factor must somehow be removed for vascularisation to proceed.

1.5 Summary

Cartilage damage in the knee is an invariable feature of ageing that may, in some instances, be hard to distinguish from cases of osteoarthritis. While extensive work has been conducted on the possible pathogenesis of osteoarthritis, the same degree of effort has not been extended in determining the factors responsible for the development of age-related changes. It is possible that the same factors are involved, such as changes in cartilage biochemistry, in the subchondral plate structure or vascularity, or in the nature of the trabecular network.

It has been hypothesized that cartilage damage can result from mechanical factors, but whether these factors act on the hyaline cartilage alone, or whether it is their action on other components of the joint which renders cartilage vulnerable to damage remains unclear. If focal contacts are involved in the remodelling of the subchondral plate, and this remodelling process involves changes in the calcified zone, tidemark, and osteochondral junction, examination of these structures as well as of the underlying cancellous bone, may provide some insight into the aetiology of the age-related changes in cartilage.

Against this background the aims of this study are the following :

(1) Determine and quantify the age-related changes throughout the knee, providing a base line for further studies and to assist in the differentiation of ageing and disease states.

(2) Examine the effect of ageing on a number of the factors that have been proposed to play a role in the development of cartilage damage in osteoarthritis, namely the calcified cartilage, subchondral vascularity, subchondral bone density and the presence of trabecular microfractures within cancellous bone, and determine whether these factors have a role in the development of age-related cartilage changes.

(3) Determine whether differences in these factors can explain the differences in the degree of damage seen between various regions within the knee.

CHAPTER 2 : METHODS AND MATERIALS

The knee was selected as the object of study because of the high incidence of degenerative change, and because it provided the opportunity to study two joints in close proximity to one another but with quite different functions.

2.1 Outline of study

Specimens were obtained as pairs of intact knee joints from autopsy cases. All knees were initially examined macroscopically and the pattern of degenerative changes recorded. One joint from each pair of knees was allocated to Group One, the microscopic arm of the study, and the other joint was allocated to Group Two, the macroscopic arm (Figure 2.1).

In Group One, blocks for histological examination were obtained, enabling the assessment of cartilage condition, the quantitation of the features of bone-cartilage interface and of the cancellous bone.

Group Two specimens were used to determine the overall distribution of focal contacts within separate regions of the knee, as well the distribution and number of trabecular microfractures.

Mapping of macroscopic cartilage damage was conducted in specimens from both Groups One and Two, in all 6 regions of the knee - the medial and lateral femoral condyles, the medial and lateral tibial facets, the trochlea and the patella.

Histological examination, focal contact and trabecular microfracture mapping were restricted to the trochlea, patella, medial femoral condyle and medial tibial facet. The medial compartment of the tibiofemoral joint was selected as it is the compartment of highest loading and most frequent degenerative changes [51].
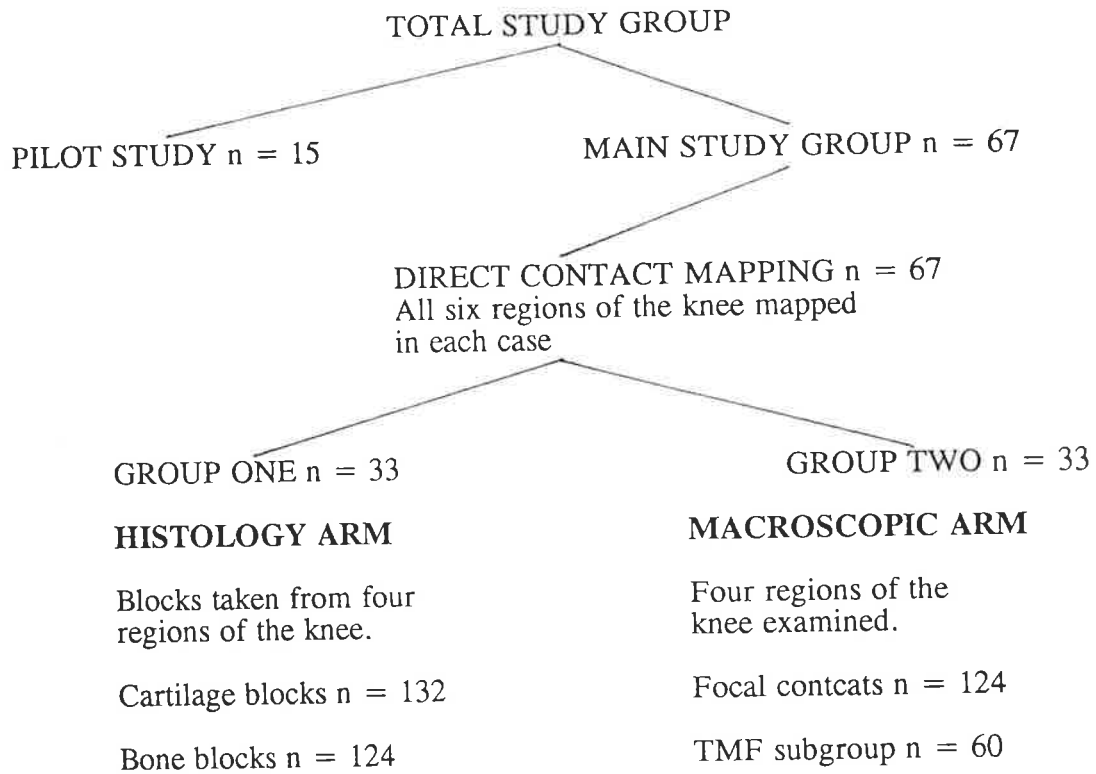
Figure 2.1 : Outline of Study

TOTAL STUDY GROUP

PILOT STUDY n = 15   MAIN STUDY GROUP n = 67

DIRECT CONTACT MAPPING n = 67
All six regions of the knee mapped
in each case

GROUP ONE n = 33   GROUP TWO n = 33

HISTOLOGY ARM   **MACROSCOPIC ARM**

Blocks taken from four   Four regions of the
regions of the knee.   knee examined.

Cartilage blocks n = 132   Focal contcats n = 124

Bone blocks n = 124   TMF subgroup n = 60

Table 2.1 : Causes of Death in the patient population

Ischaemic Heart Disease	20
Septicaemia / Meningitis	10
Ruptured Aortic Aneurysm	3
Pulmonary Emboli	3
Gastrointestinal Haemorrhage	3
Trauma / Suicide	2
Subarachnoid Haemorrhage	1
TOTAL	**42**

2.2 Specimen Selection

A total of 82 knee joints were obtained from 42 individuals, 17 female and 25 male, ranging in age from 18 to 90 years with a mean age of 61.81 ± 18.2 years.

Excluded from the study were individuals known to have a history of knee disease, to have had trauma or knee surgery, or to be suffering from metabolic bone disease or disseminated malignancy. The causes of death are listed in Table 2.1.

Specimens were removed during autopsy by dissecting away the soft tissues, sectioning the femur and tibia at 7 to 10 centimetres from the tibiofemoral joint surface and disarticulating the tibiofibular joint.

The first 15 specimens, obtained from 6 males and 2 females, ranging in age from 49 to 83 years, comprised a pilot study during which a number of technical procedures were refined and developed for use during the main study.

2.3 Specimen Preservation

In the pilot study, all specimens were stored intact, frozen at minus 20 degrees Celsius. Concerns were raised regarding the possibility of freezing artefacts in histological specimens, thus in the main study the specimens in Group One were immediately disarticulated and placed in 10% neutral formalin. The specimens in Group Two continued to be preserved by freezing although they too were disarticulated before storage. Fixation complicated the process of focal contact mapping in Group Two and was thus not considered appropriate for this group.

2.4 Mapping of degeneration

In all specimens, surface irregularities and cartilage damage were highlighted by the use of Indian ink as described by Meachim [82]. Each region was first gently cleaned, before Indian ink was liberally but gently applied to the cartilage, allowed to dry and the excess ink then removed by rinsing with normal saline. The cartilage surface was carefully examined without any magnification and

the nature and extent of degenerative changes noted. For the purpose of this study such changes were classified as slight, moderate or severe fibrillation, bone exposure, fibrocartilage or osteophyte formation (Table 2.2).

Mapping in the pilot study was done free-hand by examining each region through a clear 0.5 centimetre grid and drawing the observed areas on a similar grid. This technique was difficult, time consuming and inaccurate since the curvature of the articular surfaces was not taken into consideration. As a result, a direct contact mapping technique was developed which involved the application of strips of clear adhesive tape to the articular surface, marking the borders of the articular surface and the extent of any cartilage changes therein. The strip was then removed and applied to a piece of white paper. By marking the extent of each strip on the cartilage and repeating this process along the articular surface, a composite map of the entire surface was obtained (Figure 2.2). The maps were quantitated using an Hewlett Packard 9874A digitiser interfaced with a Hewlett Packard Series 200 computer (Hewlett Packard, Fort Collins, U.S.A.). The areas of degeneration were measured and expressed as percentages of the total articular area.

2.5 Cartilage Histology

When the articular surfaces had been mapped, the medial tibia and femur of the Group One specimens were cut into 5 millimetre thick coronal slices and the trochlea and patella were cut into 5 millimetre thick vertical slices using a band saw.

The plane of sectioning of the four regions was changed after the pilot study: the tibia and femur were cut coronally and the patella and trochlea were cut trans-axially. This was more in keeping with previous studies of the hip and presented a more open and clearly defined trabecular network for study in the femur and tibia.

Blocks for histological examination of cartilage and bone were obtained from the most central slices in the four regions of the knee that were examined (Figure 2.3).

Table 2.2 : Criteria for Assessing Macroscopic Cartilage   Condition

Intact Cartilage	Cartilage surface smooth; tangential layer intact; no uptake of Indian ink.
Slight Fibrillation	Superficial fraying of the cartilage surface; slight staining by Indian ink.
Moderate Fibrillation	More extensive fraying of cartilage; dark staining with Indian ink; no marked loss in cartilage thickness.
Severe Fibrillation	Crabmeat fibrillation of cartilage, extending deep into matrix; marked thinning of cartilage with dark staining, matt appearance.
Fibrocartilage	Smooth surfaced material, similar to hyaline cartilage in appearance, but much harder. Typically in areas of advanced articular change.
Bone exposure	Full thickness cartilage loss with exposure of underlying bone, with or without eburnation.
Osteophytes	Peripheral fibrocartilaginous or bony growths from the articular surface.

Figure 2.2 :

Above :   Photograph of the right patella of a 38 year old male. Indian ink has been applied to highlight surface irregularities in preparation for direct contact mapping. Magnification x 2.

Below :   Direct Contact map of the same specimen.

☐   Intact Cartilage

⊡   Slight Fibrillation
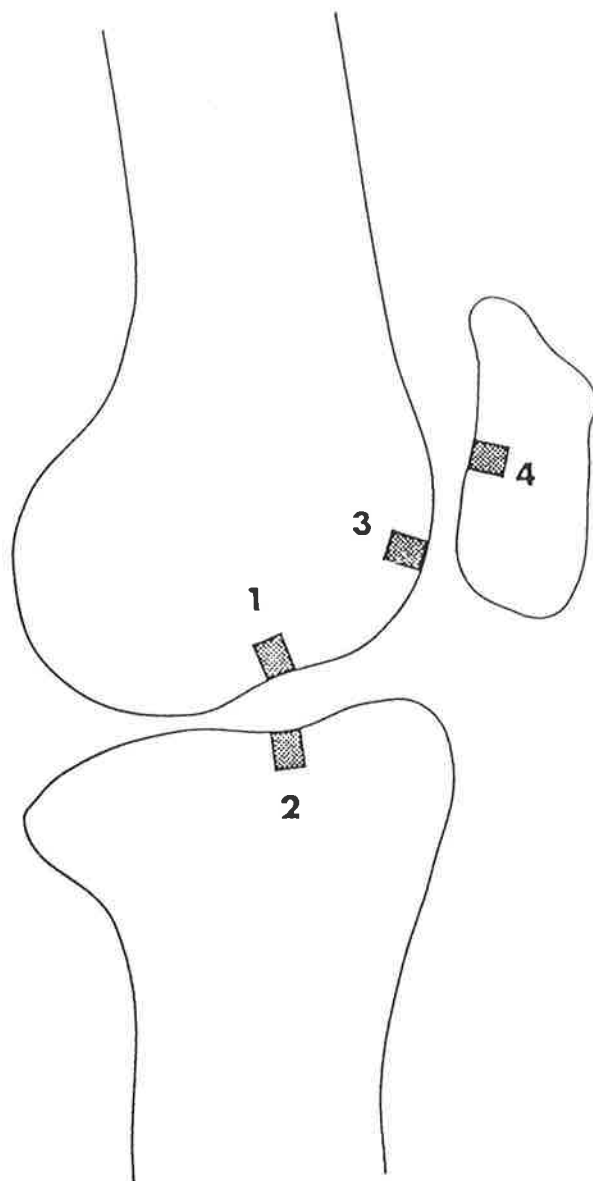
▨   Moderate Fibrillation

▨   Severe Fibrillation
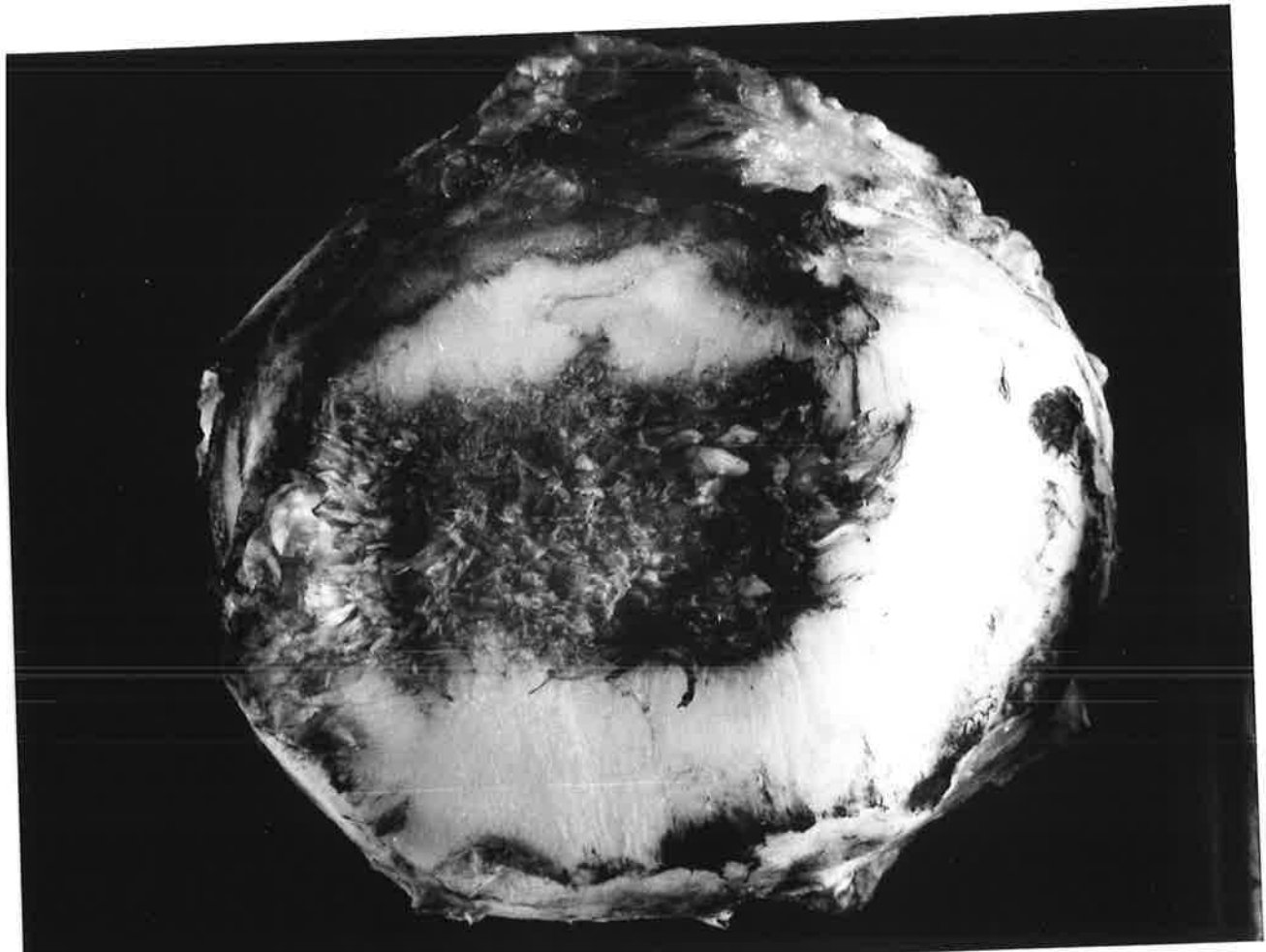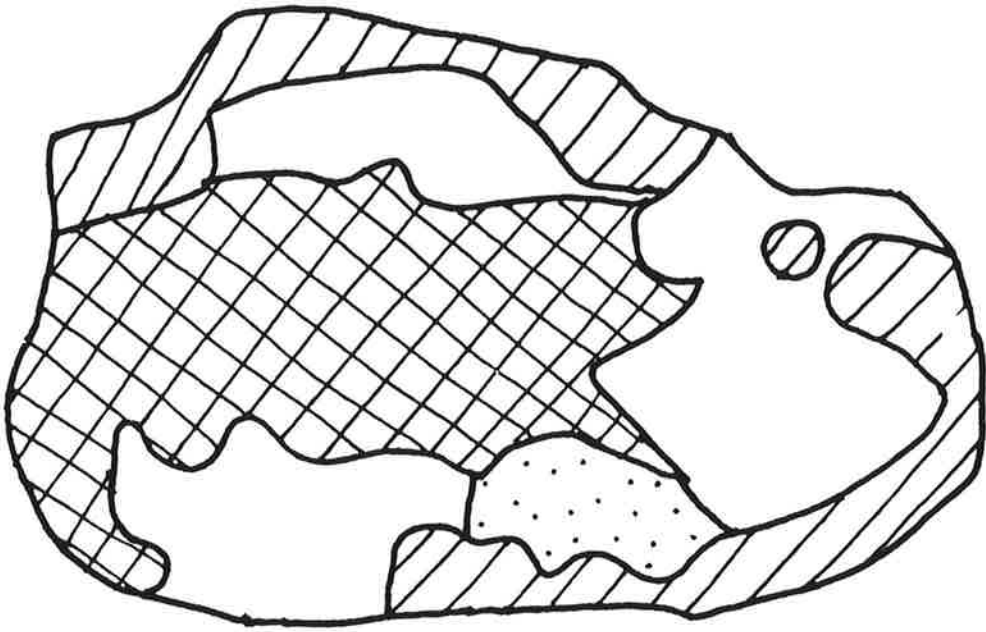
Figure 2.3 : Schematic representation of the knee joint showing the sites from which specimens were obtained for histological examination.

1 - Medial Femur
2 - Medial Tibia
3 - Trochlea
4 - Patella

In the pilot study the two most central slices were selected and the most medial of these provided blocks for cartilage histology. In the main study, the most anterior or superior slice was selected from each region.

Blocks approximately 1.5 centimetre by 1.0 centimetre were cut from the central zone of each slice using an Isomet slow speed saw (Buehler, Lake Bluff, U.S.A.). They were decalcified in a mixture of 1% ethylene diamene tetra-acetic acid and 9.5% nitric acid before being processed into paraffin. Five micron sections were cut, mounted and one section was stained with Safranin O and one with Alcian blue, acid fuchsin and eosin in the technique described by Sayers et al [120].

The condition of the hyaline cartilage was assessed using the Mankin score, which is a combination of histochemical and histological criteria [73] (Table 2.3). The score was developed for use on Safranin O stained sections, and comparison with scores obtained from the Alcian Blue stained sections showed a significant difference on paired t-test ($p < 0.0001$) and an error of 12%. There was, however, a significant positive correlation between the Safranin O and Alcian Blue scores ($r = 0.8038$, $p < 0.001$, $n = 132$). In the main study only the Alcian Blue results were considered since repeated assessments of Alcian Blue sections found no significant difference, whilst repeated assessments of Safranin O sections found an error of 23%. The Alcian Blue sections also provided clear delineation of the features at the bone-cartilage interface and was well adapted to the requirements of the image analyser.

The Quantimet Image Analysing Computer 520 (Cambridge Instruments, Cambridge, U.K.) was used to measure a number of features in the decalcified blocks. The image was relayed from an Olympus BH2 microscope, via a video camera, to the television screen of the Quantimet, and varying degrees of magnification were used to measure different features.

Total cartilage thickness, comprising both hyaline and calcified cartilage thickness was measured at 2 x objective magnification. The area of cartilage was outlined on the video screen using a cursor, the area determined, and the procedure

Table 2.3 : Mankin criteria for the assessment of cartilage condition in histological blocks.

I. Structure a. Normal b. Surface irregularities c. Pannus and surface irregularities d. Clefts to transitional zone e. Clefts to radial zone f. Clefts to calcified zone g. Complete disorganisation	0 1 2 3 4 5 6
II. Cells a. Normal b. Diffuse hypercellularity c. Cloning d. Hypocellularity	0 1 2 3
III. Safranin O Staining a. Normal b. Slight reduction c. Moderate reduction d. Severe reduction e. No dye noted	0 1 2 3 4
IV. Tidemark Integrity a. Intact b. Crossed by blood vessels	0 1

repeated to include the entire section. The mean thickness was determined by dividing the area by the length of the section (Figure 2.4).

The density and the thickness of the subchondral plate were measured to a depth of 1 millimetre below the osteochondral junction, from images at 4 x objective magnification (Figure 2.4). This method was chosen because of the poorly defined nature of the subchondral plate in the specimens studied, especially those from the tibia such that the edge of the plate adjacent to the marrow space was hard to determine in an accurate and repeatable manner.

Images at 10 x objective magnification were used to measure the mean thickness of the calcified cartilage layer and also to determine the length of both the tidemark and osteochondral junction and express them as ratios of the true length, providing a measure of the irregularity of these structures (Figure 2.4). When measuring calcified cartilage thickness and tidemark irregularity, in cases with multiple tidemarks, the tidemark nearest the articular surface was used.

The maximum number of tidemarks seen in each block was noted as was the number of vascular focal contacts, as described by Woods et al [153], per 5 fields at 40 x objective magnification.

2.6 Bone Histology

The more inferior or posterior slice of the two central slices from each region was selected to provide blocks for the histoquantitation of the cancellous bone. Blocks measuring 1.0 by 1.5 centimetres were cut from the central zone using an Isomet slow speed saw and were processed without decalcification and embedded in Araldite Epoxy resin (Ciba Geigy, Melbourne, Australia).

Five micron thick sections were cut from each block at 3 levels 200 microns apart, using a Jung K microtome (Reichert Jung, Heidelberg, West Germany). The sections were mounted and then stained by the Von Kossa technique with an haematoxylin and eosin counter-stain. Histoquantitation was conducted using the

Figure 2.4 : Schematic diagram of the bone-cartilage interface

$$\text{Total Cartilage Thickness} = \frac{\text{Area of hyaline and calcified cartilage}}{\text{Specimen Length}}$$
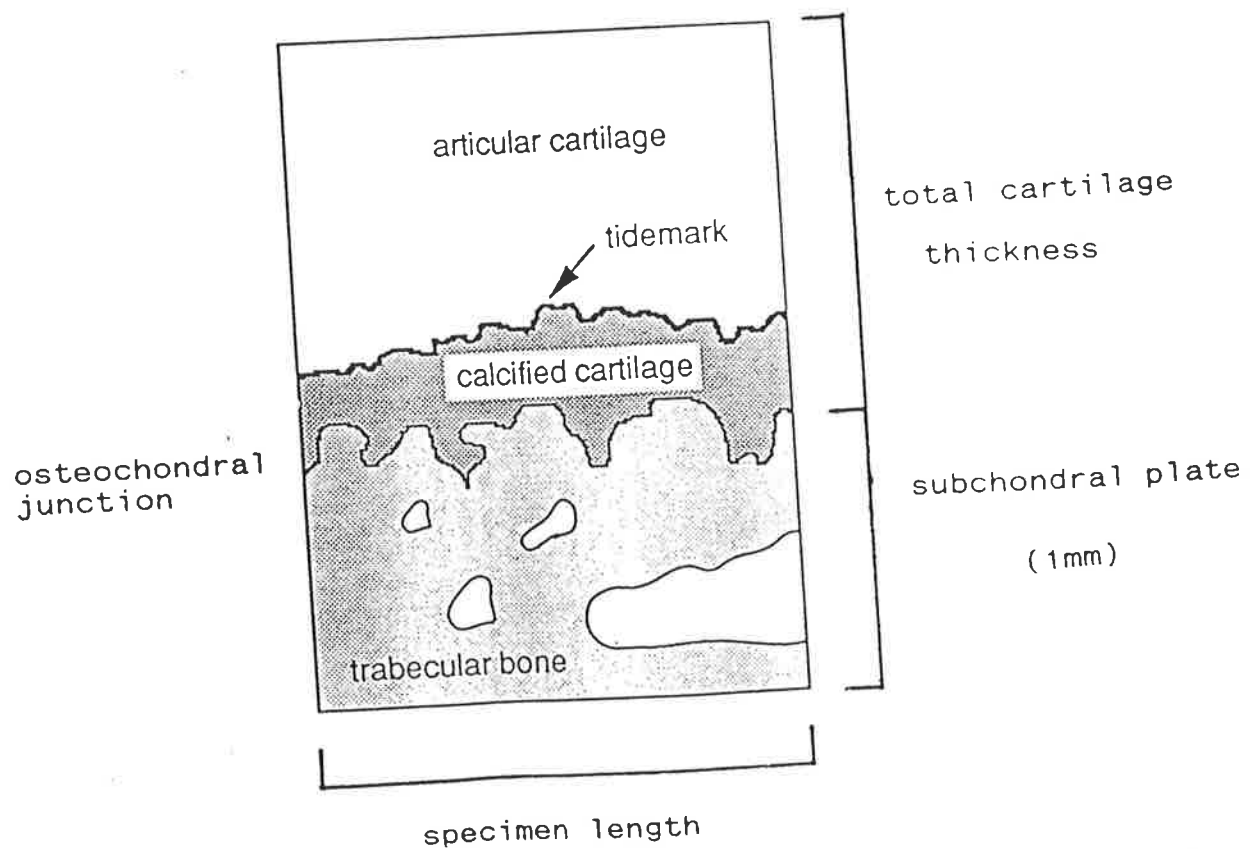
$$\text{Subchondral Plate Thickness} = \frac{\text{Area of SCP 1 mm below the OCJ}}{\text{Specimen Length}}$$

$$\text{Calcified Cartilage Thickness} = \frac{\text{Area of calcified cartilage}}{\text{Specimen Length}}$$

$$\text{Tidemark irregularity} = \frac{\text{Length of Tidemark}}{\text{Specimen Length}}$$

$$\text{Osteochondral junction} = \frac{\text{Length of Osteochondral junction}}{\text{Specimen Length}} \text{ irregularity}$$

SCP - Subchondral Plate   ; OCJ - Osteochondral Junction

Quantimet 520 Image Analyser at 10 x objective magnification and examining 20 fields per section. The parameters examined in this study were the percentage of mineral bone (BV/TV), the surface density of bone in mm^2/mm^3 (BS/TV), trabecular thickness (Tb.Th) and trabecular spacing (Tb.Sp) both in microns.

2.7 Focal contacts

The overall distribution of focal contacts throughout the medial femoral condyle, medial tibial facet, trochlea and patella was determined for all the Group Two specimens using the technique of Lane et al [69].

After the cartilage surface had been mapped, the articular surface was divided into one centimetre squares. In the pilot study this was done using measurements made directly onto the cartilage, but in the main study group a one centimetre square grid was placed over the direct contact map and the grid transferred to the articular surface using landmarks provided by the pattern of degeneration (Figure 2.5).

The layer of hyaline cartilage was then removed using a scalpel, and great care was taken to avoid removing the calcified layer. The focal contacts, apparent as small capillary-like structures on the surface, were visualised using a dissecting microscope at 10 x magnification and counted. Their number could then be expressed per square centimetre or in terms of focal contacts per mm^2 using the area obtained from digitisation of the direct contact maps. In the pilot study, the counts per square were repeated by the same observer but, since no significant difference between the repeated counts was found using a paired t-test (p > 0.7), the focal contacts were counted only once in the main study.

2.8 Trabecular Microfractures

The number and distribution of trabecular microfractures within the medial femoral condyle, medial tibial facet, trochlea and patella were assessed in a subgroup of Group Two consisting of one male and one female specimen for each
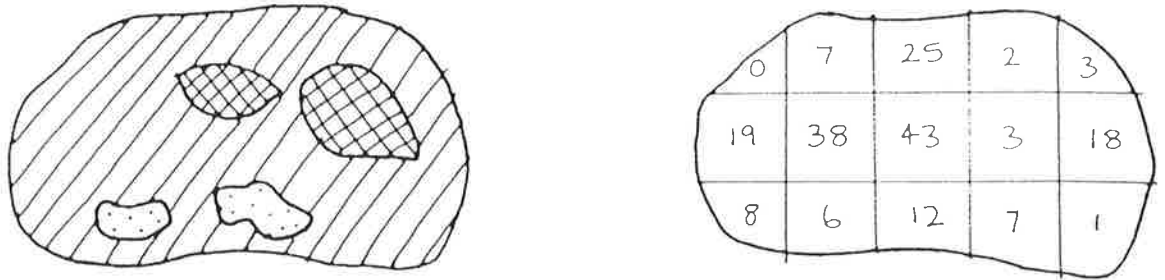
Figure 2.5 :

Left - Direct contact map of the left patella from a 69 year female.

Right - Results of the macroscopic mapping of the focal contacts visible after the removal of hyaline cartilage. Numbers represent the number of focal contacts seen within each one centimetre grid square.

☐   Intact Cartilage

▣   Slight Fibrillation

▨   Moderate Fibrillation

▩   Severe Fibrillation

decade, commencing with the decade 15 to 24. The only exception was the decade 45 to 55, where there were no females, and so two male specimens were chosen; and the 15-24 age group, where one specimen was damaged during processing.

Each of the 4 regions was cut into approximately 5 millimetre thick slices, using a band saw, with the patella and trochlea being cut in the trans-axial plane and the medial femoral condyle and medial tibial plateau being cut coronally.

The most central slices were selected from each region and were macerated by being heated to 80 degrees Celsius in a 4% solution of sodium hydroxide for 30 minutes. The remaining marrow was removed using a fine jet of hot water. They were then bleached in a 10% solution of hydrogen peroxide for up to 16 hours, air dried and then placed in petroleum spirit for 48 hours to remove any residual fat.

The slices were examined from the anterior or superior aspect using a binocular dissecting microscope at 25 x magnification.

Trabecular microfracture was considered to have occurred where there was evidence of callus formation (Figure 2.6), and the position and the orientation of the fractured trabecula was marked on a clear sheet of plastic film placed directly over the slice.

2.9 Statistical analyses

Data analysis during this study was conducted using PC-SAS software (SAS Institute Incorporated, Cary, U.S.A.).

Before any statistical comparisons were made the nature of the distribution of each data group was determined by using the Shapiro-Wilk statistic.

Comparisons in normally distributed groups was made using paired or non paired t-tests. Populations where the distribution was not normal were compared using the Wilcoxon rank statistic. Comparisons between more than two subgroups

Figure 2.6 : A healing trabecular microfracture in the femoral condyle of a 90 year old female. x 40 objective magnification.
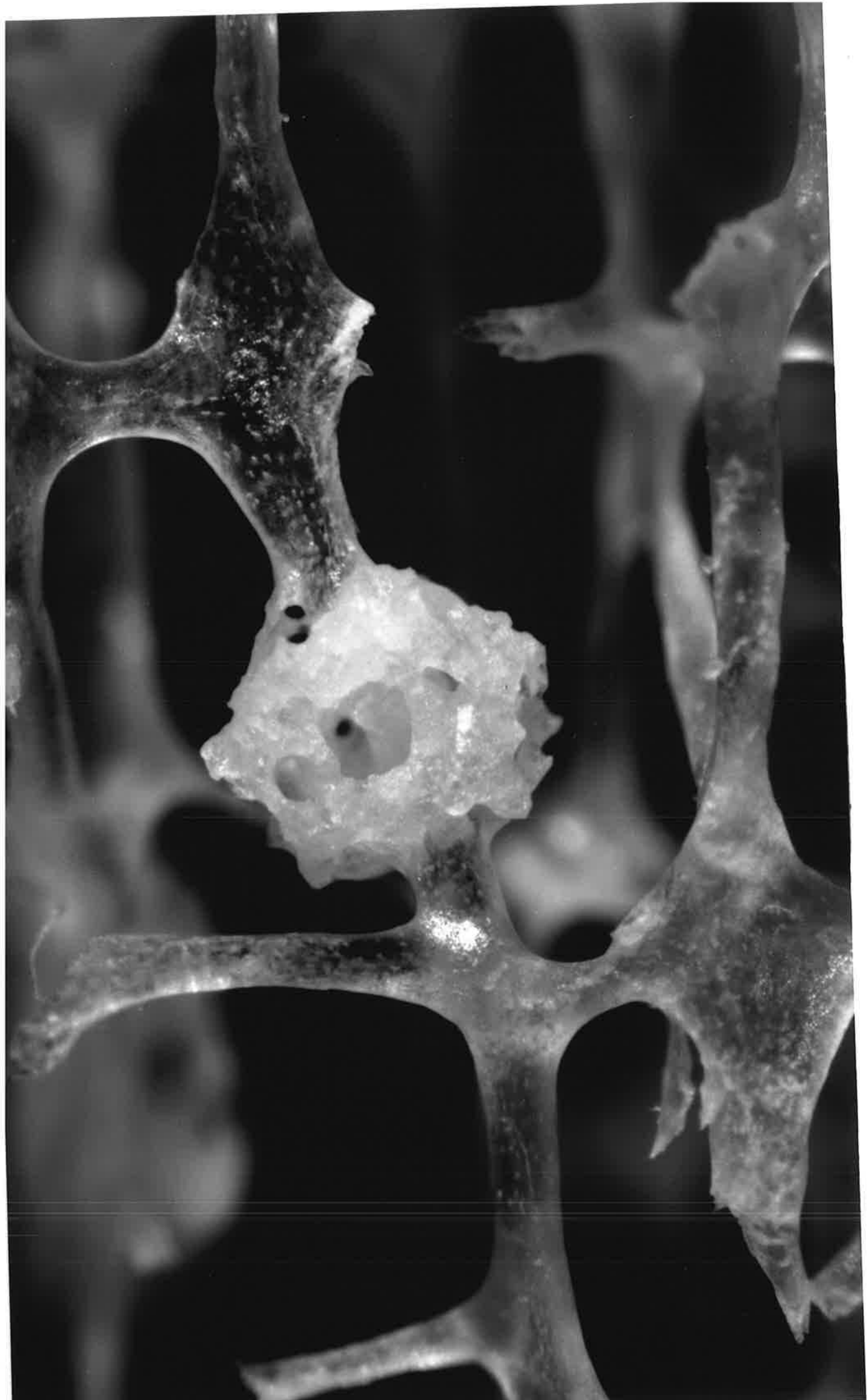
were conducted using a one way analysis of variance in normally distributed populations and multiple Wilcoxon rank tests in non-normal populations.

Correlations were conducted in normally distributed groups using the Pearson coefficient of correlation, and in non-normal populations the Spearman rank coefficient was used. Linear and non-linear regressions were conducted as indicated.

The level of significance of this study was taken to be $p < 0.05$ for all tests.

CHAPTER 3 : CARTILAGE MAPPING

Before attempting to determine the aetiology of age-related changes in the knee, it is first necessary to have a clear understanding of their pattern and distribution. In this study the distribution of degenerative changes within all compartments of the knee was determined using the Meachim Indian ink method and the direct contact mapping method described in the previous chapter. The results obtained from the macroscopic examination of the six regions of the knee are presented in two parts. Firstly, the pattern and distribution of age-related cartilage damage is described to provide an overview of the nature and extent of degenerative changes that may occur in a normal population, followed by presentation of the quantitative results obtained from digitisation of the direct contact maps.

3.1 The Pattern of Cartilage Damage in the Knee

The frequency of the various forms of cartilage damage within the six regions of the knee is seen in Table 3.1. The frequency of slight and moderate fibrillation is very similar across the regions. The patella has the highest frequency of severe fibrillation, fibrocartilage formation and bone exposure, and the lowest frequency of osteophyte formation. The lateral femoral condyle has the lowest frequency of severe fibrillation, fibrocartilage formation and bone exposure, whilst the medial tibial plateau has the highest frequency of osteophyte formation. Advanced changes such as fibrocartilage formation, bone exposure and osteophyte formation are seen more frequently in females than in males in most regions (Table 3.2).

An overview of the extent of the possible cartilage changes that may occur has been provided by using, as examples, the least degenerated and most degenerated specimens in each of eight ten-year age groups, beginning with the

Table 3.1 : Frequency of the various forms of cartilage damage within the six regions of the knee. Table represents the percentage of cases with each form of cartilage change. Total n = 82.

LOCATION	SL	M	S	FC	BE	OP
M.F.	100	90	55	11	7	16
L.F.	99	84	17	9	1	15
M.T.	100	85	27	2	5	20
L.T.	99	88	56	28	4	15
TROC	100	90	44	20	7	11
PAT	99	93	59	28	10	4

Table 3.2 : Frequency of advanced forms of cartilage change by region and gender. Values given are the percent of the population exhibiting the various forms of cartilage change. Males n = 50; Females n = 32.

	SEVERE		F.C		B.E.		O.P	
	M	F	M	F	M	F	M	F
MF	58	50	4	22	4	13	8	28
LF	18	16	8	9	0	3	8	25
MT	24	31	0	6	2	9	12	31
LT	52	63	18	44	2	6	4	31
TR	48	38	12	31	8	6	6	19
PA	60	56	20	41	8	13	2	6

SL - Slight Fibrillation
M - Moderate Fibrillation
S - Severe Fibrillation
FC - Fibrocartilage
BE - Bone Exposure
OP - Osteophytes
M - Males

MF - Medial Femoral Condyle
LF - Lateral Femoral Condyle
MT - Medial Tibial Plateau
LT - Lateral Tibial Plateau
TROC - Trochlea
PAT - Patella
F - Females

decade 15 to 24. Each region of the knee has been divided into zones, which were used to localise the cartilage changes seen within each region, and which were based on a combination of anatomical and functional considerations (Figure 3.1)

The femoral condyles have been divided into 5 zones : an anterior and a posterior third, and a central third which has been divided into medial, central, and lateral zones (Figure 3.1).

3.1.1 The Medial Femoral Condyle

The specimen in the age group 15-24 in Figure 3.2, obtained from a 22 year old male, is an example of a normal medial condyle, where the cartilage surface was intact apart from small, discrete areas of slight fibrillation around the periphery. The least degenerated specimens within each age group (Figure 3.2) displayed little variation. The typical pattern consisted of areas of slight and moderate fibrillation in the anterior zone, adjacent to the trochlea and along the lateral or inner border of the condyle as seen in the specimen from the age group 35-44. Although fissures were seen in the central weight bearing zone in the age group 55-64, severe fibrillation was not seen until the next decade. Widespread damage of the central weight bearing areas was not seen until the 85-94 age group. Areas of fibrocartilage, bone exposure and osteophytes were not seen in any of the specimens.

In contrast, examination of the most degenerated specimens (Figure 3.3) revealed that, while the pattern of cartilage damage was similar to that of the least damaged specimens in the early age groups, severe fibrillation occurred at a much earlier age, being present in the decade 35-44, as did widespread damage of the central zone as can be seen in age group 55-64. Osteophytes, bone exposure and fibrocartilage were seen from the 65-74 age group and onwards.

Figure 3.1 : The division of the six regions of the knee for the purposes of description of the pattern of macroscopic cartilage damage.
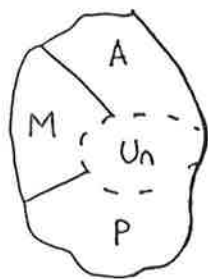
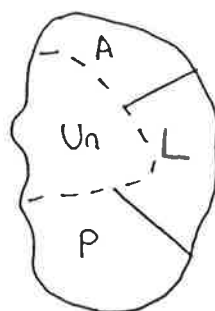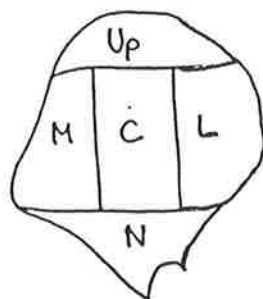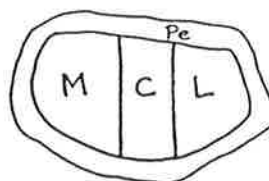| Zones : | A - Anterior | Un - Uncovered |
	M - Medial	Up - Upper
	C - Central	N - Notch
	L - Lateral	Pe - Periphery
	P - Posterior	

MEDIAL FEMUR   LATERAL FEMUR

MEDIAL TIBIA   LATERAL TIBIA

TROCHLEA   PATELLA

Figure 3.2 : Contact maps of the least degenerated medial femoral condyles for each decade, commencing 15 - 24 years.

M - Male ; F - Female ; R - Right ; L - Left.

☐ - Intact Cartilage

⬓ - Fissures

⬚ - Slight Fibrillation

▨ - Moderate Fibrillation

▧ - Severe Fibrillation

▦ - Fibrocartilage formation

■ - Bone exposure

▩ - Osteophyte formation

15-24 M 22 (R) 25-34 M 28 (L) 35-44 F 35 (L)

45-54 M 48 (L) 55-64 M 55 (L) 65-74 M 72 (R)
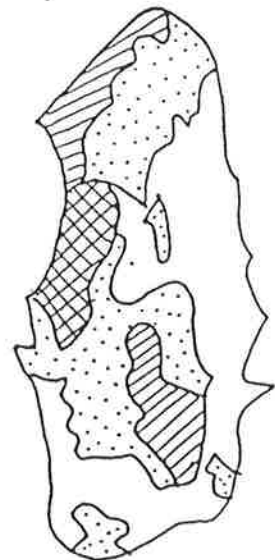
75 - 84 F 81 (L) 85-94 M 85 (R)
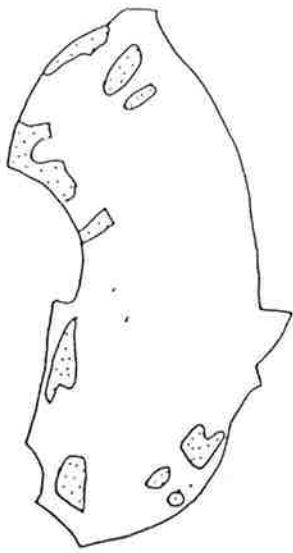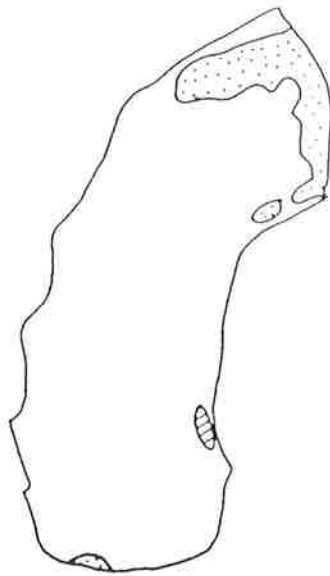
Figure 3.3 : Contact maps of the most degenerated medial femoral condyles for each decade, commencing 15 - 24 years.
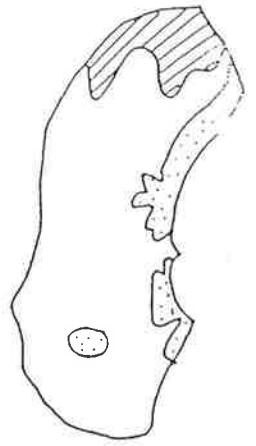
M - Male ; F - Female ; R - Right ; L - Left.

☐ - Intact Cartilage

〰 - Fissures

⬚ - Slight Fibrillation

▨ - Moderate Fibrillation

⧆ - Severe Fibrillation

▨ - Fibrocartilage formation

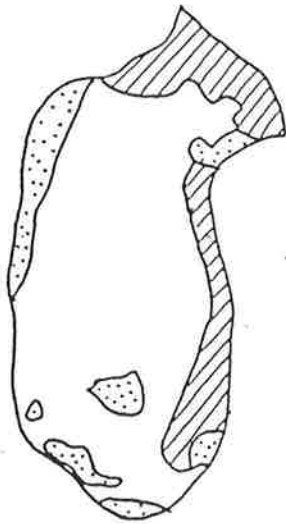■ - Bone exposure

▨ - Osteophyte formation
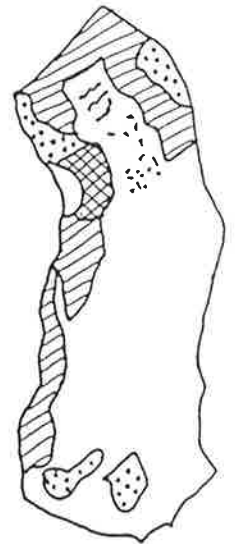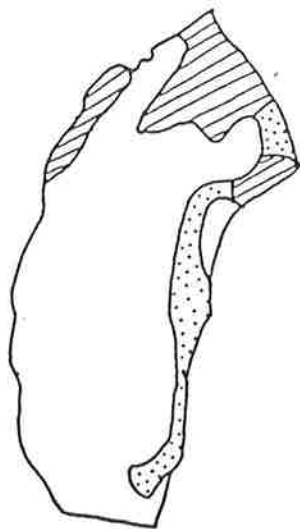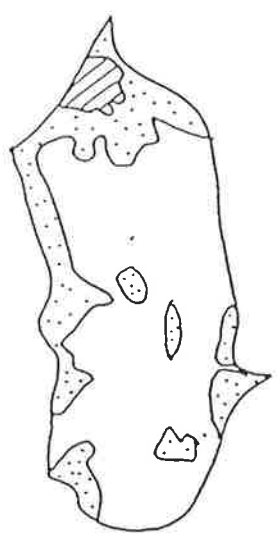
25-34 F 34 (R)　　　35-44 M 43 (R)　　　45-54 M 48 (L)
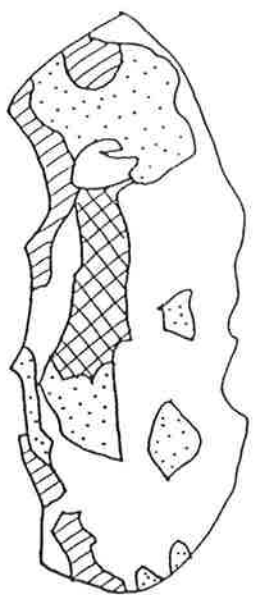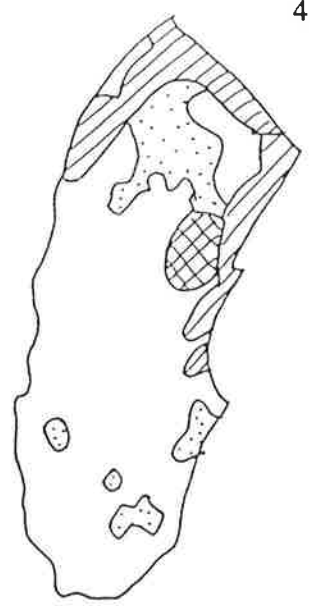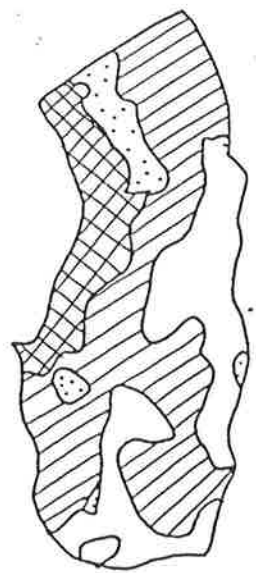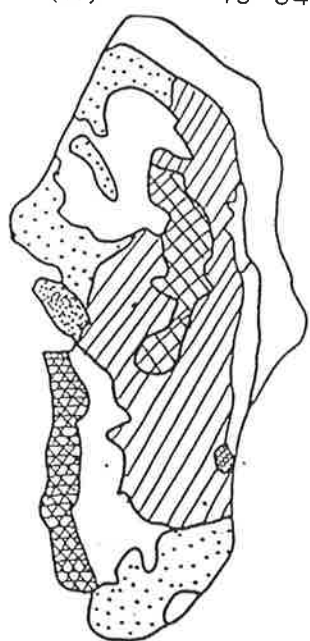
55-64 M 63 (R)　　　65-74 M 68 (R)
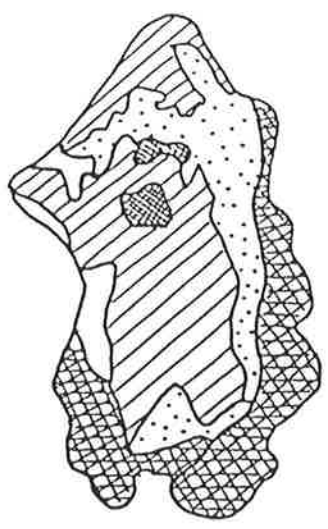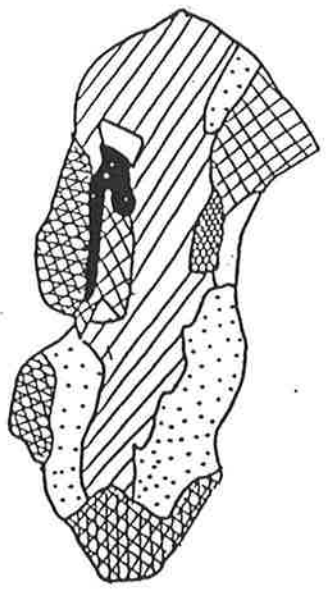
75 - 84 F 78 (R)　　85-94 F 90 (L)

The results from examination of the total study group are seen in Table 3.3. The anterior zone is most typically affected by slight and moderate fibrillation. The inner, lateral aspect of the medial condyle is by far the most frequent area to be affected by severe fibrillation, although bone exposure was not seen here in any specimen. Full thickness loss and bone exposure were seen in the anterior, medial and central zones only. Fibrocartilage formation was seen in all areas except the anterior zone, and was most frequent in the posterior zone.

3.1.2 The Lateral Femoral Condyle

The specimen in the age group 15-24 in the least degenerated specimens (Figure 3.4) provided an example of a normal lateral femoral condyle, with the cartilage surface essentially intact apart from small, scattered areas of slight fibrillation.

In the least damaged specimens from each decade (Figure 3.4), degenerative changes appeared restricted to the periphery of the condyle, especially the anterior and medial zones in the younger age groups. Fissures extending from the medial zone to the central zone were seen in the decade 45-54, but extensive involvement of the central zone was not seen until the age group 65-74. Severe fibrillation, bone exposure and osteophytes were not evident in any specimen, although an area of fibrocartilage was seen in the posterior zone of the condyle of the specimen in age group 85-94.

No such restriction of degenerative changes to the periphery was evident in the most degenerated specimens (Figure 3.5). By the decade 35-44, severe fibrillation was seen in the central zone, and fibrocartilage and osteophytes were seen in the 45-54 age group. Areas of fibrocartilage were seen in all subsequent age groups except for the decade 65-74. An area of bone exposure was seen in the specimen from the 75-84 age group.

Table 3.3 : Age prevalence of features within the various zones of the medial femoral condyle. Figures represent the actual number of specimens.

Age in years as decades commencing 15 to 24 years old.

The values for the frequency of fibrocartilage (FC) and bone exposure (BE) are given for all age groups combined.

SLIGHT FIBRILLATION

Age	15-24	-34	-44	-54	-64	-74	-84	-94	TOTAL
Cases	4	4	8	8	12	21	21	4	82
ANTERIOR	1	1	2	3	1	6	6	-	20
MEDIAL	1	-	1	5	4	10	10	2	33
POSTERIOR	2	2	2	4	3	8	6	-	27
LATERAL	3	1	4	1	3	1	8	-	21
CENTRAL	-	1	6	6	7	8	11	-	39

MODERATE FIBRILLATION

Age	15-24	-34	-44	-54	-64	-74	-84	-94	TOTAL
Cases	4	4	8	8	12	21	21	4	82
ANTERIOR	2	3	5	4	11	10	15	3	58
MEDIAL	-	-	1	1	-	3	5	-	10
POSTERIOR	-	-	1	-	8	9	13	2	33
LATERAL	1	3	1	4	7	10	6	1	33
CENTRAL	-	-	-	-	2	3	1	4	10

SEVERE FIBRILLATION

| Age	15-24	-34	-44	-54	-64	-74	-84	-94	TOTAL		FC	BE
Cases	4	4	8	8	12	21	21	4	82	::	82	82
ANTERIOR	-	-	-	1	-	3	-	1	5	::	-	3
MEDIAL	-	-	1	-	-	2	1	1	5	::	1	2
POSTERIOR	-	-	-	1	-	3	1	-	5	::	4	-
LATERAL	-	-	2	3	2	9	6	2	24	::	2	-
CENTRAL	-	-	1	-	-	9	5	1	16	::	3	1

Figure 3.4 : Contact maps of the least degenerated lateral femoral condyles for each decade, commencing 15 - 24 years.

M - Male ; F - Female ; R - Right ; L - Left.

☐ - Intact Cartilage

〰 - Fissures

▦ - Slight Fibrillation

▨ - Moderate Fibrillation

▩ - Severe Fibrillation

▩ - Fibrocartilage formation

■ - Bone exposure

▩ - Osteophyte formation
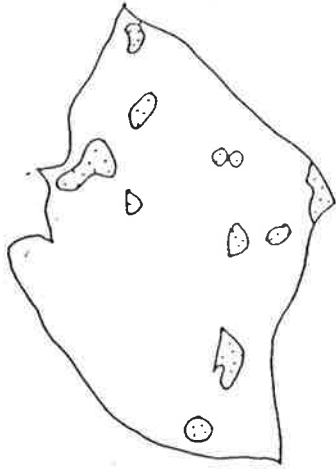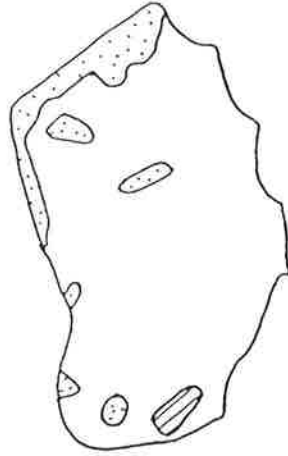
15-24 M 22 (R)　　25-34 M 28 (L)　　35-44 F 35 (L)
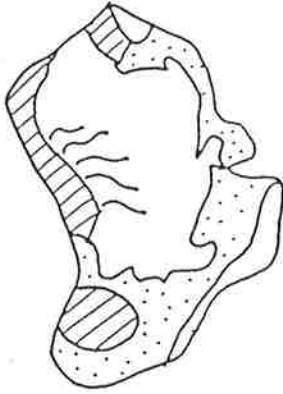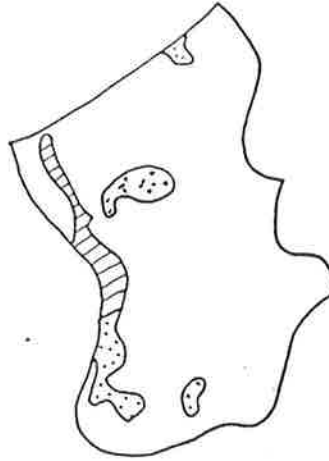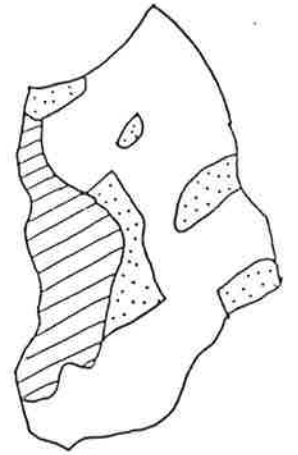
45-54 M 46 (L)　　55-64 M 55 (L)　　65-74 M 72 (L)
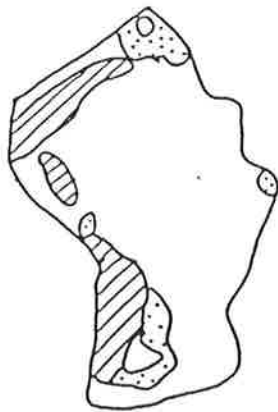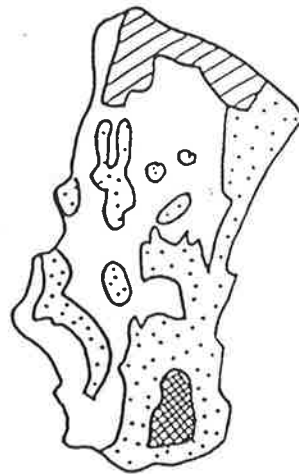
75 - 84 F 81 (L)　　85-94 M 85 (R)

Figure 3.5 : Contact maps of the most degenerated lateral femoral condyles for each decade, commencing 15 - 24 years.

M - Male ; F - Female ; R - Right ; L - Left.

☐ - Intact Cartilage

〰 - Fissures

▦ - Slight Fibrillation

▨ - Moderate Fibrillation

▩ - Severe Fibrillation

▨ - Fibrocartilage formation

■ - Bone exposure

▨ - Osteophyte formation
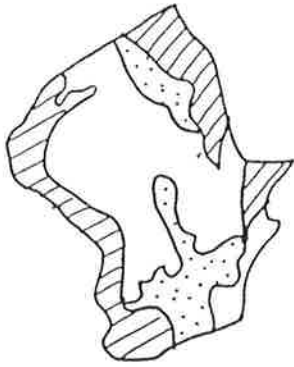
25-34 F 34 (L)
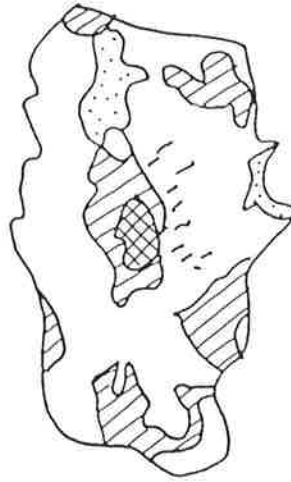
35-44 M 43 (R)
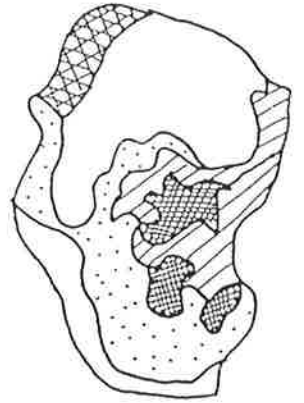
45-54 M 46 (R)
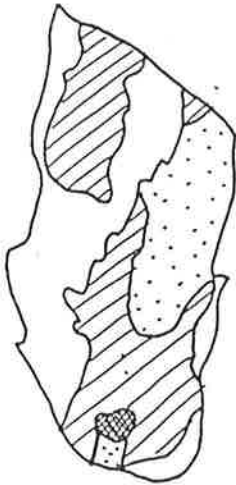
55-64 M 63 (R)
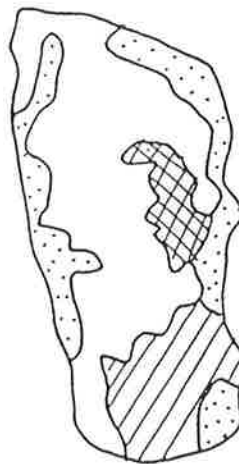
65-74 F 74 (R)
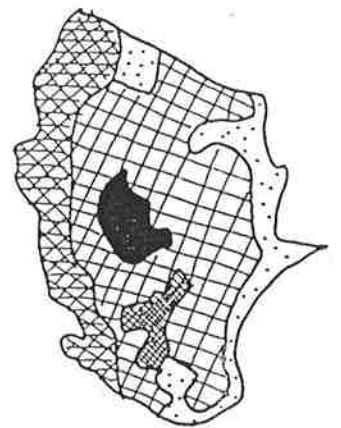
75-84 F 78 (R)
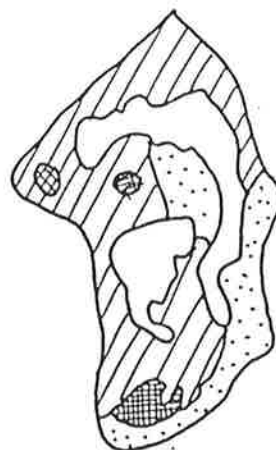
85-94 F 90 (L)

The least degenerated and most degenerated lateral condyles in each decade are distinguished not only by the degree of cartilage damage, but also in the distribution of damage, with extensive involvement of the central zone being seen only in the most degenerated group.

The data from the entire study are shown in Table 3.4. Slight and moderate fibrillation are the most common forms of cartilage damage in all zones of the lateral femoral condyle. Severe fibrillation and fibrocartilage formation are most frequent in the posterior zone, but full thickness loss and bone exposure was seen in the central zone in only one specimen.

3.1.3 The Medial Tibial Plateau

The medial tibial plateau has been divided into a meniscal covered area consisting of anterior, medial and posterior zones, and the central uncovered zone (Figure 3.1).

Degenerative changes were restricted to scattered areas of slight fibrillation in and around the uncovered zone in the age groups 15-24 and 25-34 in the least degenerated specimens (Figure 3.6). Confluent areas of slight and moderate fibrillation were more extensive in older age groups, so that by the decade 85-94, there was very little intact cartilage in the uncovered zone. Changes in the covered zones were restricted to small areas of slight fibrillation. In no specimens were there areas of severe fibrillation, fibrocartilage or bone exposure, although in the 85-94 age group there was a small osteophyte in the posterior zone.

Extensive involvement of the uncovered area by slight and moderate fibrillation was evident from the age group 25-34 and onwards in the most degenerated specimens (Figure 3.7). Osteophyte formation was seen in the 35-44 age group, but osteophytes were not seen otherwise until the decade 75-84. Severe fibrillation and bone exposure were seen after the decade 55-64. Extensive

Table 3.4 : Age prevalence of features within the various zones of the lateral femoral condyle. Figures represent the actual number of specimens.

Age in years as decades commencing 15 to 24 years old.

The values for the frequency of fibrocartilage (FC) and bone exposure (BE) are given for all age groups combined.

SLIGHT FIBRILLATION

Age	15-24	-34	-44	-54	-64	-74	-84	-94		TOTAL
Cases	4	4	8	8	12	21	21	4		82
ANTERIOR	4	2	6	7	6	14	6	–		45
MEDIAL	2	1	2	1	6	8	6	2		28
POSTERIOR	1	1	3	4	4	5	3	–		21
LATERAL	4	3	7	5	3	14	9	3		48
CENTRAL	2	3	7	4	6	10	6	2		40

MODERATE FIBRILLATION

Age	15-24	-34	-44	-54	-64	-74	-84	-94		TOTAL
Cases	4	4	8	8	12	21	21	4		82
ANTERIOR	–	2	2	1	5	6	9	4		29
MEDIAL	2	1	6	6	6	10	10	1		42
POSTERIOR	–	3	5	3	3	14	9	1		38
LATERAL	–	1	–	–	–	2	2	1		6
CENTRAL	–	–	–	–	2	3	3	1		9

SEVERE FIBRILLATION

| Age	15-24	-34	-44	-54	-64	-74	-84	-94		TOTAL		FC	BE
Cases	4	4	8	8	12	21	21	4		82		82	82
ANTERIOR	–	–	–	–	–	–	1	–		1		–	–
MEDIAL	–	–	–	–	–	2	–	1		3		2	–
POSTERIOR	–	–	–	1	2	–	2	–		5		6	–
LATERAL	–	–	–	–	–	–	1	–		1		–	–
CENTRAL	–	–	1	–	–	1	1	–		3		3	1

Figure 3.6 : Contact maps of the least degenerated medial tibial plateaux for each decade, commencing 15 - 24 years.

M - Male ; F - Female ; R - Right ; L - Left.
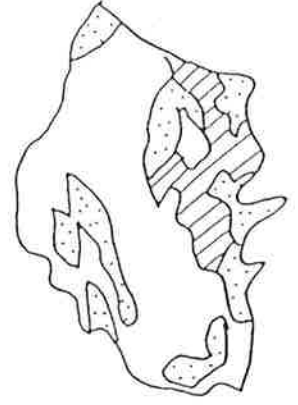
☐ - Intact Cartilage

� - Fissures

▦ - Slight Fibrillation

▨ - Moderate Fibrillation

▩ - Severe Fibrillation

▓ - Fibrocartilage formation

■ - Bone exposure

▩ - Osteophyte formation
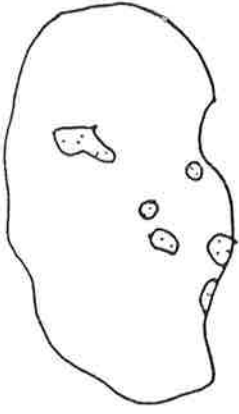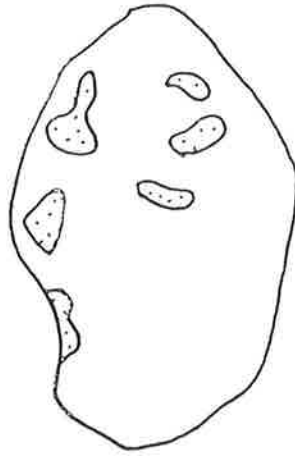
15-24 F 18 (R)   25-34 M 28 (L)   35-44 F 35 (L)
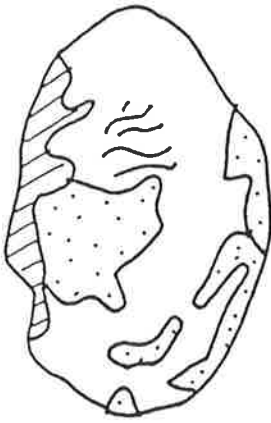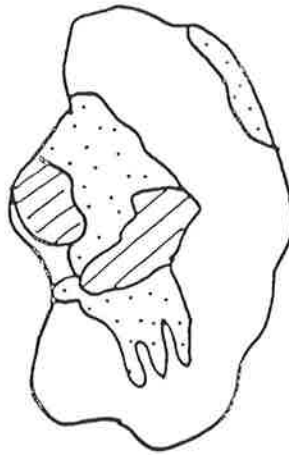
45-54 M 46 (L)   55-64 M 55 (L)   65-74 F 65 (R)
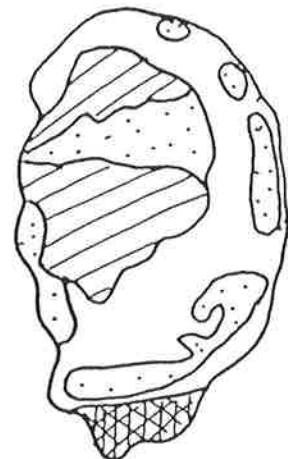
75-84 F 81 (R)   85-94 M 85 (L)

Figure 3.7 : Contact maps of the most degenerated medial tibial plateaux for each decade, commencing 15 - 24 years.

M - Male ; F - Female ; R - Right ; L - Left.

☐ - Intact Cartilage

〰 - Fissures

▢ - Slight Fibrillation

▨ - Moderate Fibrillation

▧ - Severe Fibrillation

▦ - Fibrocartilage formation

■ - Bone exposure

▨ - Osteophyte formation

15-24 M 22 (L)   25-34 F 34 (L)   35-44 M 43 (R)
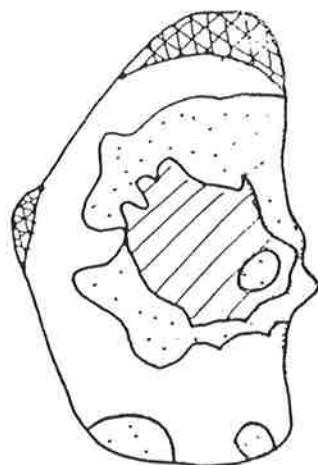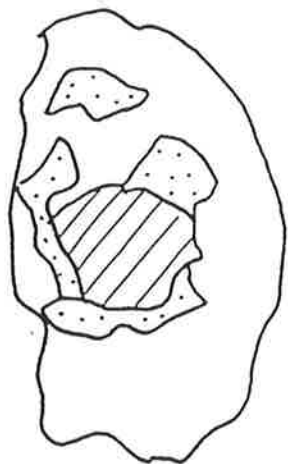
45-5·4 M 48 (L)   55-64 M 63 (R)   65-74 M 68 (L)
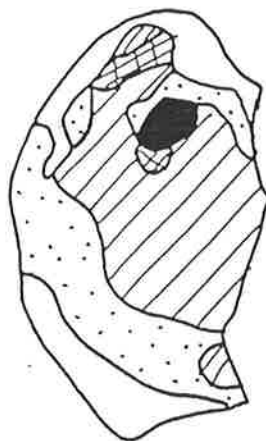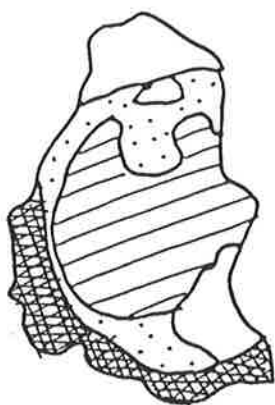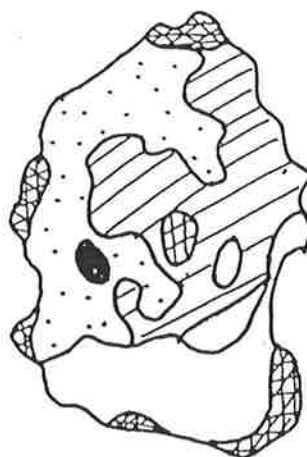
75-84 F 78 (R)   85-94 F 90 (R)

involvement of the covered zones was evident in specimens from the decade 55-64 and in older age groups.

Thus, it can be seen that the least affected and most severely affected specimens for age were differentiated not so much by the distribution of cartilage damage but by the severity of such damage. All specimens showed the concentration of advanced cartilage changes such as severe fibrillation in the uncovered, central zone.

Slight fibrillation was most common in the medial and posterior covered zones of the medial tibial plateau, whilst moderate and severe fibrillation were most common in the uncovered zone (Table 3.5). Bone exposure was seen in the uncovered zone in only two cases.

3.1.4 The Lateral Tibial Plateau

The lateral tibial plateau was divided into an uncovered zone, not covered by the meniscus, and a covered area consisting of anterior, lateral and posterior zones (see Figure 3.1).

The earliest changes consisted of discrete areas of slight fibrillation in the uncovered zone in the least degenerated specimens (Figure 3.8), as seen in the specimen in the 15-24 age group. Involvement of the uncovered zone by both slight and moderate fibrillation increased with age and almost total involvement of the area was seen by the decade 45-54. Severe fibrillation was seen for the first time in the decade 65-74. Scattered areas of slight fibrillation were seen in the anterior and lateral covered zones in all age groups. Areas of severe fibrillation in the posterior covered zone were seen as early as the decade 35-44, whilst fibrocartilage was not seen until the 65-74 age group. A posterior osteophyte was seen in the age group 85-94.

In the most degenerated specimens (Figure 3.9) the uncovered zone displayed extensive areas of moderate fibrillation after the decade 55-64. Transverse

Table 3.5 : Age prevalence of features within the various zones of the medial tibial plateau. Figures represent the actual number of specimens.

Age in years as decades commencing 15 to 24 years old.

The values for the frequency of fibrocartilage (FC) and bone exposure (BE) are given for all age groups combined.

SLIGHT FIBRILLATION

Age	15-24	-34	-44	-54	-64	-74	-84	-94		TOTAL
Cases	4	4	8	8	12	21	21	4		82
UNCOVERED	3	1	3	2	4	1	1	-		15
ANTERIOR	1	1	5	3	5	11	10	1		37
MEDIAL	2	3	4	3	7	11	12	1		43
POSTERIOR	-	3	4	6	6	12	9	1		40

MODERATE FIBRILLATION

Age	15-24	-34	-44	-54	-64	-74	-84	-94		TOTAL
Cases	4	4	8	8	12	21	21	4		82
UNCOVERED	1	3	5	6	8	13	10	3		49
ANTERIOR	-	-	-	2	3	2	10	3		20
MEDIAL	-	-	1	2	3	3	5	3		17
POSTERIOR	-	-	1	2	3	5	6	3		20

SEVERE FIBRILLATION

Age	15-24	-34	-44	-54	-64	-74	-84	-94		TOTAL		FC	BE
Cases	4	4	8	8	12	21	21	4		82	::	82	82
UNCOVERED	-	-	-	-	-	6	9	-		15	::	-	2
ANTERIOR	-	-	-	-	1	2	-	-		3	::	-	-
MEDIAL	-	-	-	-	-	2	-	-		2	::	-	-
POSTERIOR	-	-	-	-	-	2	-	-		2	::	-	-

Figure 3.8 : Contact maps of the least degenerated lateral tibial

plateaux for each decade, commencing 15 - 24 years.

M - Male ; F - Female ; R - Right ; L - Left.

☐ - Intact Cartilage

▨ - Fissures

▨ - Slight Fibrillation

▨ - Moderate Fibrillation

▨ - Severe Fibrillation

▨ - Fibrocartilage formation

■ - Bone exposure

▨ - Osteophyte formation
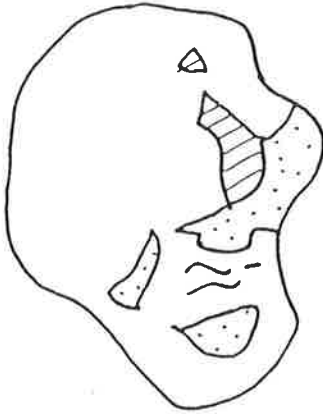
15-24 F 18 (R)   25-34 M 28 (L)   35-44 F 35 (L)
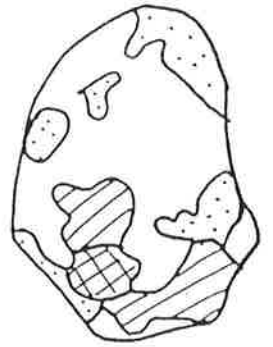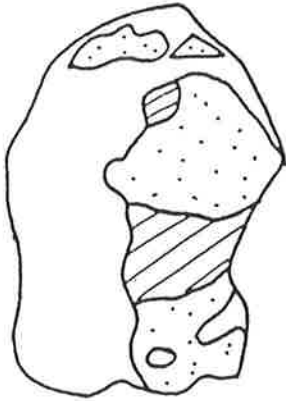
45-54 M 48 (L)   55-64 M 55 (L)   65-74 F 65 (R)
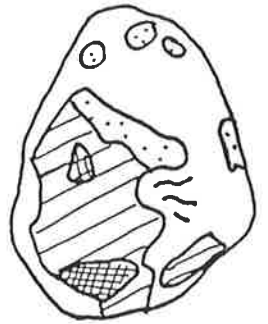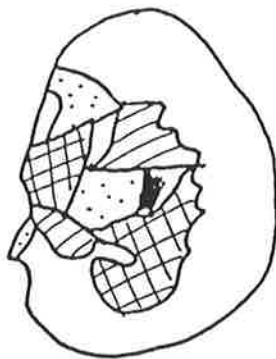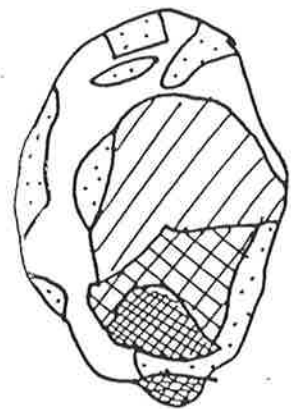
75-84 F 81 (R)   85-94 M 85 (L)

Figure 3.9 : Contact maps of the most degenerated lateral tibial

plateaux for each decade, commencing 15 - 24 years.

M - Male ; F - Female ; R - Right ; L - Left.

☐ - Intact Cartilage

〰 - Fissures

▣ - Slight Fibrillation

▨ - Moderate Fibrillation

▩ - Severe Fibrillation

▦ - Fibrocartilage formation

■ - Bone exposure

▩ - Osteophyte formation
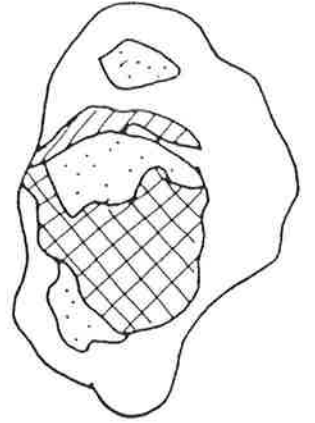
15-24 M 22 (L)　　　25-34 F 34 (L)　　　35-44 M 43 (R)
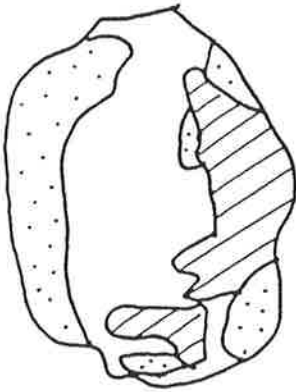
45-54 M 46 (L)　　　55-64 M 63 (R)　　　65-74 M 68 (L)
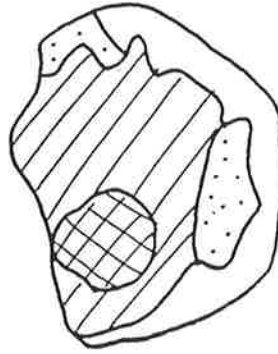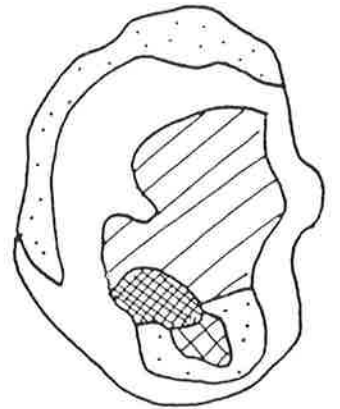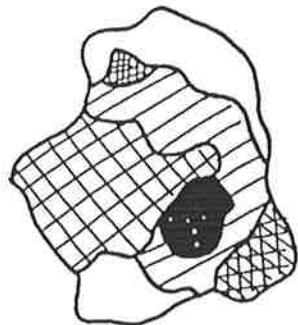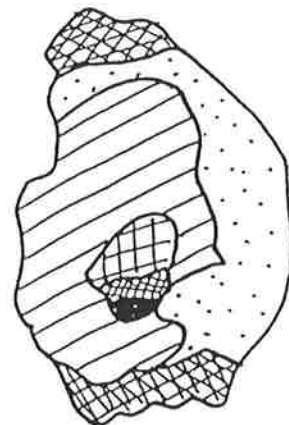
75-84 F 78 (R)　　　85-94 F 90 (R)

fissures were seen in the posterior covered zone in the youngest specimen, and in the posterior and lateral zones in the 25-34 decade. Severe fibrillation was evident in the posterior zone in the age group 35-44, and either fibrocartilage or bone exposure were present in the posterior zone after, and including, the decade 65-74. Osteophytes were seen in the lateral area in the specimen from the 75-84 age group, and in the anterior and posterior zones of the specimen from the 85-94 age group.

The least degenerated and most degenerated specimens in each age group were distinguished by the severity of the cartilage changes rather than by differences in distribution. All specimens tended to have advanced cartilage changes such as severe fibrillation, fibrocartilage formation and bone exposure limited to the central uncovered and the posterior zones.

The anterior and lateral covered zones of the lateral tibia were most frequently affected by slight and moderate fibrillation. Severe fibrillation was seen far more frequently in the uncovered and posterior covered zones than elsewhere (Table 3.6). Fibrocartilage formation and bone exposure were seen only in the posterior covered zone, and 28 % of specimens studied had fibrocartilage in this zone.

3.1.5 The Trochlea

The trochlea was divided into upper, medial, lateral and central zones, and a notch, or intercondylar, zone (Figure 3.1).

The pattern of degeneration in the younger specimens of the least damaged specimens (age groups 15-24 and 25-34, Figure 3.10) consisted of discrete scattered areas of slight and moderate fibrillation, typically involving the upper and notch zones. This pattern appeared unchanged until the decade 35-44, although the areas affected increased with age. In the decades 45-54 and 55-64, the severity of cartilage damage did not increase but the areas of moderate and slight fibrillation

Table 3.6 : Age prevalence of features within the various zones of the lateral tibial plateau. Figures represent the actual number of specimens.

Age in years as decades commencing 15 to 24 years old.

The values for the frequency of fibrocartilage (FC) and bone exposure (BE) are given for all age groups combined.

SLIGHT FIBRILLATION

Age	15-24	-34	-44	-54	-64	-74	-84	-94		TOTAL
Cases	4	4	8	8	12	21	21	4		82
UNCOVERED	4	1	2	4	3	3	1	–		18
ANTERIOR	1	3	5	5	6	13	9	3		55
LATERAL	–	1	5	3	3	10	10	4		36
POSTERIOR	2	4	–	–	1	–	–	–		7

MODERATE FIBRILLATION

Age	15-24	-34	-44	-54	-64	-74	-84	-94		TOTAL
Cases	4	4	8	8	12	21	21	4		82
UNCOVERED	–	3	5	4	7	11	5	1		36
ANTERIOR	–	–	1	1	6	6	10	1		25
LATERAL	–	–	–	1	6	5	7	–		19
POSTERIOR	–	–	1	5	7	3	3	–		12

SEVERE FIBRILLATION

| Age	15-24	-34	-44	-54	-64	-74	-84	-94		TOTAL		FC	BE
Cases	4	4	8	8	12	21	21	4		82	::	82	82
UNCOVERED	–	–	1	–	2	7	15	3		28	::	–	–
ANTERIOR	–	–	–	–	–	–	2	–		2	::	–	–
LATERAL	–	–	–	–	–	–	1	–		1	::	–	–
POSTERIOR	–	–	6	3	2	6	8	–		27	::	23	3

Figure 3.10 : Contact maps of the least degenerated trochleas for each decade, commencing 15 - 24 years.
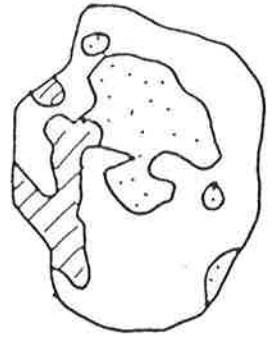
M - Male ; F - Female ; R - Right ; L - Left.

☐ - Intact Cartilage

〜 - Fissures

⬚ - Slight Fibrillation

▨ - Moderate Fibrillation

▩ - Severe Fibrillation

▨ - Fibrocartilage formation

■ - Bone exposure

▨ - Osteophyte formation
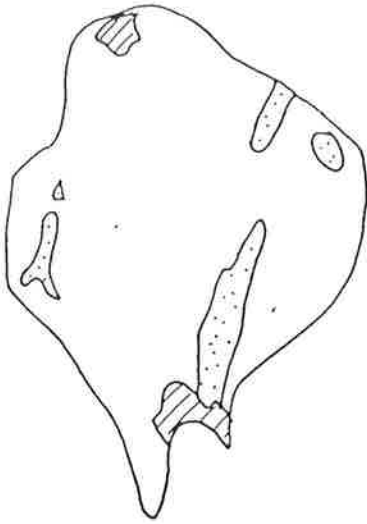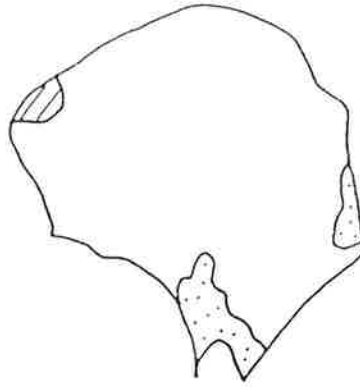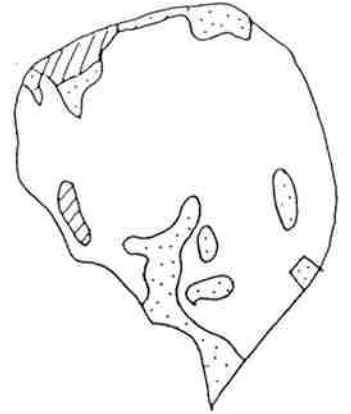
15-24 M 22 (R)　　　　25-34 M 28 (L)　　　　35-44 M 43 (L)
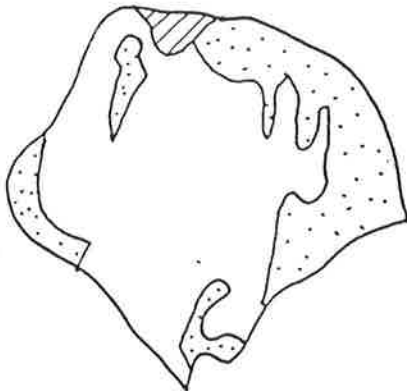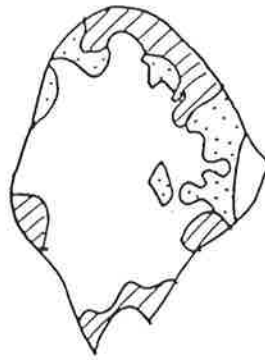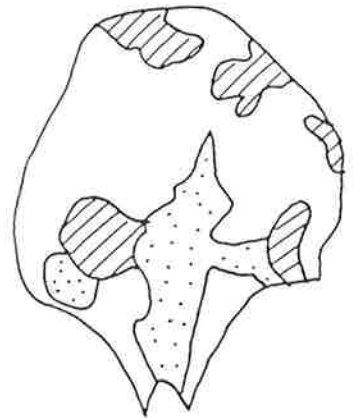
45-54 M 50 (R)　　　　55-64 F 64 (R)　　　　65-74 M 68 (R)
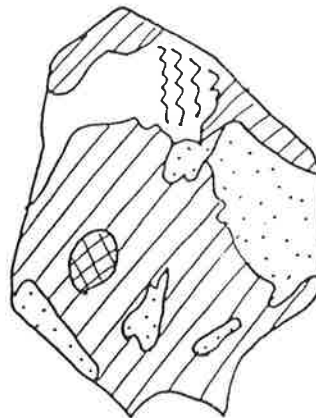
75-84 F 81 (L)　　　　85-94 M 85 (R)

became confluent. Widespread involvement of the central zone was not seen until the decade 65-74 and severe fibrillation was not seen until the decade 85-94.

In contrast in the most degenerated specimens (Figure 3.11), severe fibrillation was seen in a much younger age group (45-54 years), as was widespread involvement of the central zone. Bone exposure was evident in the specimen from the age group 55-64, and areas of fibrocartilage and osteophyte formation were seen in the trochlea from the decade 75-84 years.

The least and most degenerated specimens were clearly differentiated by the widespread, often severe, involvement of the central zone seen in the more degenerated cases after the decade 45-54.

The results from all 82 specimens examined can be seen in Table 3.7. The most common forms of cartilage damage were slight and moderate fibrillation. Severe fibrillation, fibrocartilage formation and bone exposure were seen most frequently in the central zone of the trochlea. Fibrocartilage formation and severe fibrillation were seen in all areas of the trochlea, but full thickness cartilage loss and bone exposure were seen only in the central, medial and lateral zones.

3.1.6 The Patella

The patella was divided into a thin peripheral zone, a central vertical ridge, and medial and lateral facets (see Figure 3.1).

In the youngest of the least damaged specimens (Figure 3.12), there were small scattered areas of slight fibrillation. Areas of slight and moderate fibrillation were restricted to the periphery until the decade 45-54, when there was involvement of the central, medial and lateral zones. The areas affected appeared to increase with age but nothing more severe than moderate fibrillation was seen until the decade 85-94 when both severe fibrillation and fibrocartilage were present.

In the most degenerated specimens (Figure 3.13), changes were not restricted to the periphery at any age and even in the youngest specimen the central

Figure 3.11 : Contact maps of the most degenerated trochleas for each decade, commencing 15 - 24 years.

M - Male ; F - Female ; R - Right ; L - Left.

☐ - Intact Cartilage

〰 - Fissures

▦ - Slight Fibrillation

▨ - Moderate Fibrillation

▧ - Severe Fibrillation   •

▦ - Fibrocartilage formation

■ - Bone exposure

▨ - Osteophyte formation
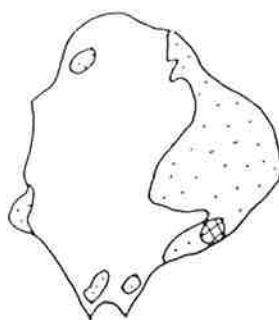
15-24 F 18 (R)   25-34 F 34 (R)   35-44 F 39 (L)
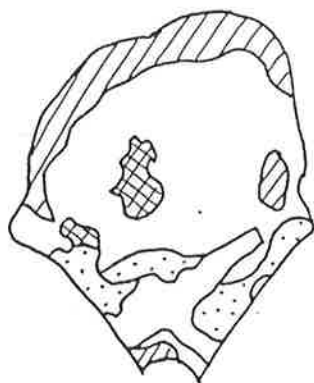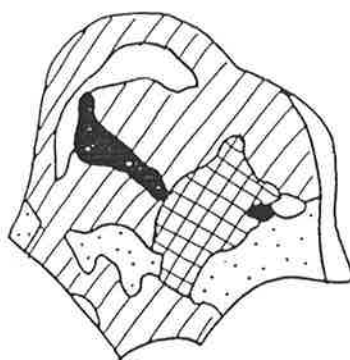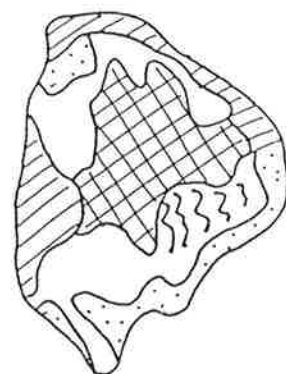
45-54 M 48 (L)   55-64 M 63 (R)   65-74 M 72 (R)
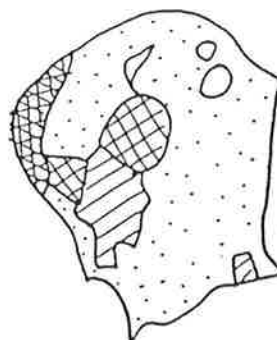
75-84 F 78 (R)   85-94 F 90 (L)

Table 3.7 : Age prevalence of features within the various zones of the trochlea. Figures represent the actual number of specimens.

Age in years as decades commencing 15 to 24 years old.

The values for the frequency of fibrocartilage (FC) and bone exposure (BE) are given for all age groups combined.

SLIGHT FIBRILLATION

Age	15-24	-34	-44	-54	-64	-74	-84	-94		TOTAL
Cases	4	4	8	8	12	21	21	4		82
UPPER	4	3	5	2	3	4	7	2		30
LATERAL	4	4	5	7	3	8	3	5		36
NOTCH	4	3	3	4	6	7	5	-		32
MEDIAL	-	3	3	3	7	6	8	-		30
CENTRAL	1	1	3	2	5	3	2	-		16

MODERATE FIBRILLATION

Age	15-24	-34	-44	-54	-64	-74	-84	-94		TOTAL
Cases	4	4	8	8	12	21	21	4		82
UPPER	-	1	2	5	8	16	6	2		40
LATERAL	-	-	1	-	1	3	7	1		13
NOTCH	-	1	4	4	6	10	6	4		35
MEDIAL	-	-	5	2	4	8	2	3		24
CENTRAL	-	-	1	1	1	8	3	2		16

SEVERE FIBRILLATION

Age	15-24	-34	-44	-54	-64	-74	-84	-94		TOTAL		FC	BE
Cases	4	4	8	8	12	21	21	4		82	::	82	82
UPPER	-	-	1	1	-	-	-	-		2	::	1	-
LATERAL	-	-	-	-	-	1	1	1		3	::	4	1
NOTCH	-	-	-	-	-	1	1	-		2	::	3	-
MEDIAL	-	-	-	2	1	2	1	-		6	::	4	1
CENTRAL	-	-	1	2	3	5	6	2		19	::	4	3

Figure 3.12 : Contact maps of the least degenerated patellas for each decade, commencing 15 - 24 years.

M - Male ; F - Female ; R - Right ; L - Left.

☐ - Intact Cartilage

〰 - Fissures

▨ - Slight Fibrillation

▨ - Moderate Fibrillation

▨ - Severe Fibrillation

▨ - Fibrocartilage formation

■ - Bone exposure

▨ - Osteophyte formation
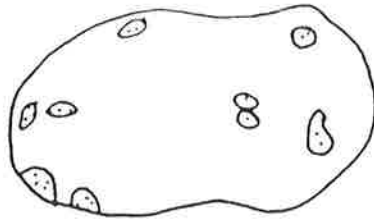
15-24 F 18 (L)
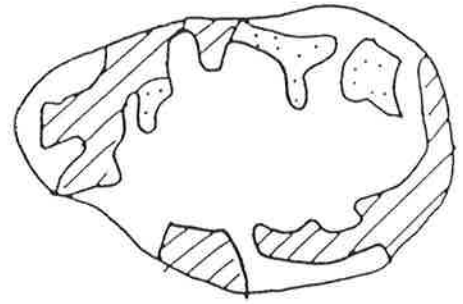
25-34 M 28 (R)
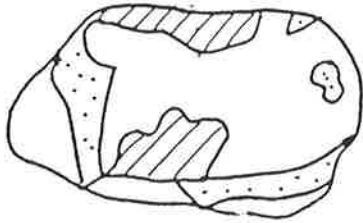
35-44 F 39 (R)
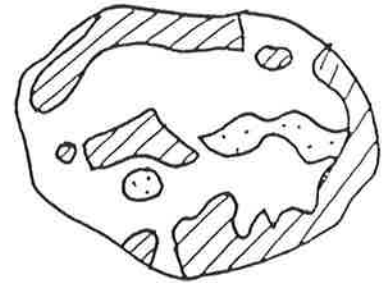
45-54 M 46 (R)
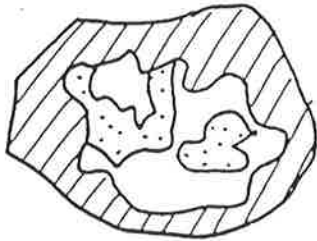
55-64 F 64 (R)
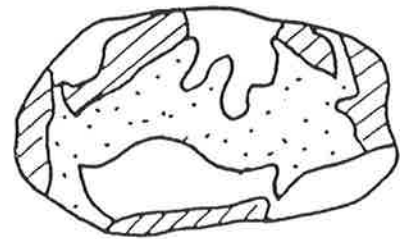
65-74 M 68 (L)
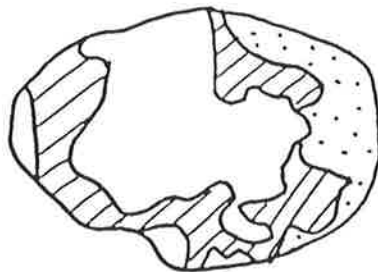
75-84 F 81 (R)
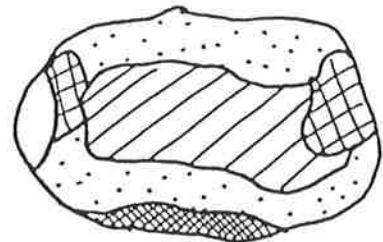
85-94 F 90 (R)

Figure 3.13 : Contact maps of the most degenerated patellas for each decade, commencing 15 - 24 years.

M - Male ; F - Female ; R - Right ; L - Left.

☐ - Intact Cartilage

〰 - Fissures

▨ - Slight Fibrillation

▨ - Moderate Fibrillation

▨ - Severe Fibrillation

▨ - Fibrocartilage formation

■ - Bone exposure

▨ - Osteophyte formation
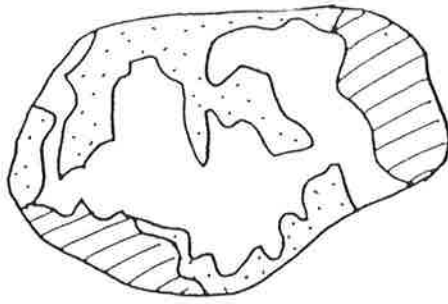
15-24 M 22 (L)
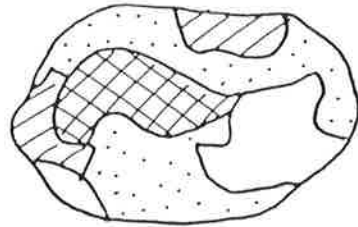
25-34 F 34 (R)
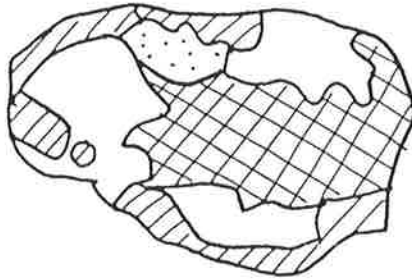
35-44 M 38 (R)
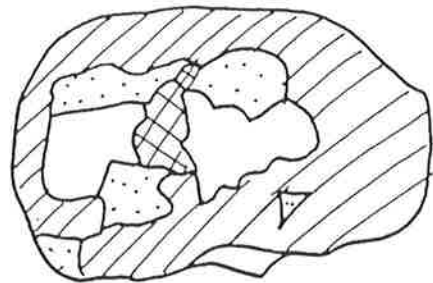
45-54 M 48 (L)
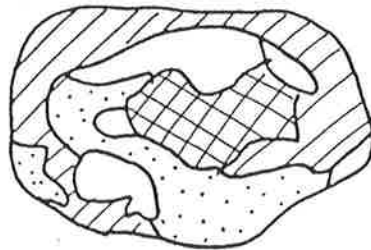
55-64 M 55 (L)
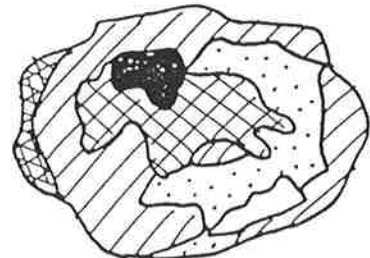
65-74 F 69 (R)
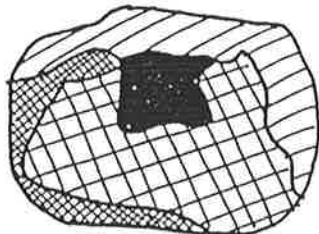
75-84 F 78 (R)
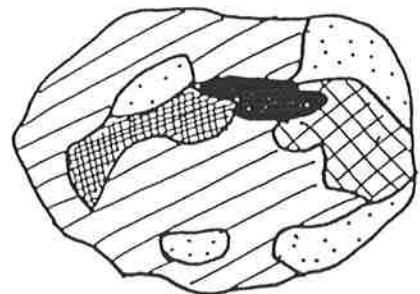
85-94 M 85 (R)

zone displayed an area of slight fibrillation. Severe fibrillation was seen from the decade 25-34 and onwards, typically as a horizontal band across the patella. By the decade 45-54, very little intact cartilage remained on the patella. Bone exposure and fibrocartilage were seen in the central and medial zones from the 65-74 age group onwards.

The least damaged specimens were easily distinguished from the most degenerated specimens at an early age, by the widespread involvement of the central, medial and lateral zones in the latter group. The results from the 82 specimens of the total study (Table 3.8) show that the periphery of the patella was most frequently affected by slight and moderate fibrillation. Severe fibrillation and fibrocartilage formation were most frequent in the medial and central facets and bone exposure was found only on the medial and central facets.

Table 3.8 : Age prevalence of features within the various zones of the patella. Figures represent the actual number of specimens.

Age in years as decades commencing 15 to 24 years old.

The values for the frequency of fibrocartilage (FC) and bone exposure (BE) are given for all age groups combined.

SLIGHT FIBRILLATION

Age	15-24	-34	-44	-54	-64	-74	-84	-94		TOTAL
Cases	4	4	8	8	12	21	21	4		82
MEDIAL	–	1	3	1	–	4	1	–		10
CENTRAL	4	2	4	3	2	4	1	–		20
LATERAL	1	3	4	7	2	4	2	–		23
PERIPHERY	1	1	1	2	2	3	1	1		12

MODERATE FIBRILLATION

Age	15-24	-34	-44	-54	-64	-74	-84	-94		TOTAL
Cases	4	4	8	8	12	21	21	4		82
MEDIAL	2	2	4	7	6	6	7	–		34
CENTRAL	–	–	2	3	9	5	5	–		24
LATERAL	–	–	2	1	7	11	10	2		33
PERIPHERY	3	3	7	6	10	17	19	3		68

SEVERE FIBRILLATION

Age	15-24	-34	-44	-54	-64	-74	-84	-94		TOTAL		FC	BE
Cases	4	4	8	8	12	21	21	4		82	::	82	82
MEDIAL	–	1	–	–	6	7	10	1		25	::	6	3
CENTRAL	–	2	2	2	1	8	12	2		29	::	3	5
LATERAL	–	–	1	–	3	4	9	1		18	::	1	–
PERIPHERY	–	–	–	–	–	1	1	–		2	::	–	–

3.2 Quantitation of Cartilage Mapping

Digitisation of the direct contact maps from the 67 specimens of the main study allowed the total surface area of each region to be calculated in square millimetres. The various forms of degeneration within each region were expressed as percentages of the total area.

Results for the main study, that is from all six regions of the knee from all 67 specimens mapped using the direct contact method, can be seen in Table 3.9.

3.2.1 Male - Female Comparison

The mean age of the male subgroup, 57.82 ± 17.5 years, was not significantly different to the mean age of the female subgroup, 62.07 ± 21.1 years, on Wilcoxon rank testing ($p > 0.20$).

All six regions of the knees obtained from males were significantly larger in area than those obtained from females (Table 3.10). Knees from males also had a significantly greater percentage area of intact cartilage in the total study group ($p < 0.03$), and in all regions of the knee except for the medial tibial plateau and the patella where no significant difference in the percentage area of intact cartilage was seen between the sexes (Table 3.11).

When considering the various forms of cartilage damage in the total study group, it was found that females had significantly greater percentage areas of moderate fibrillation, fibrocartilage, bone exposure and osteophytes (Table 3.12). No significant male - female differences were seen in the areas of slight or severe fibrillation.

The difference in the state of the articular cartilage between the sexes was greatest in the medial femoral condyle, where females displayed significantly greater areas of slight fibrillation, moderate fibrillation, fibrocartilage and osteophytes, and a significantly smaller area of intact cartilage. The gender-related

Table 3.9 : Table of the mean values for joint surface area and the percent areas affected by the various forms of cartilage damage in the main study group. Values are given as mean ± standard deviation.

VARIABLE	MEAN ± S.D.
Surface area (mm^2)	1777.38 ± 532.5
% Area Intact Cartilage	53.38 ± 19.2
% Area Slight Fibrillation	21.55 ± 13.2
% Area Moderate Fibrillation	18.87 ± 16.2
% Area Severe Fibrillation	3.23 ± 7.0
% Area Fibrocartilage	0.81 ± 2.3
% Area Bone Exposure	0.25 ± 1.7
% Area Osteophytes	1.63 ± 5.0

Table 3.10 : The surface area in millimetres square of each region of the knee in males and females. Mean ± Standard Deviation.

Region	Males n = 39	Females n = 28	p
M.F.	2684.97 ± 340.5	2309.01 ± 369.8	< 0.001
L.F.	2153.15 ± 275.2	1781 ± 232.6	< 0.001
M.T.	1539.02 ± 162.3	1268.07 ± 209.4	< 0.001
L.T.	1456.73 ± 157.5	1148.18 ± 153.2	< 0.001
TR	2226.39 ± 280.3	1735.72 ± 193.9	< 0.001
PAT	1512.47 ± 174.7	1156.86 ± 158.0	< 0.001

M.F. - Medial Femur   M.T. - Medial Tibia
L.F. - Lateral Femur   L.T. - Lateral Tibia
TR - Trochlea   PA - Patella

Table 3.11 : The percentage areas of intact cartilage in each area of the knees, in males and females of the main study group. M.F. - Medial Femur; M.T. - Medial Tibia; L.F. - Lateral Femur; L.T. - Lateral Tibia; TR - Trochlea; PA - Patella

Region	Males n = 39	Females n = 28	p
M.F.	66.95 ± 16.1	48.78 ± 27.2	< 0.005
L.F.	68.91 ± 16.2	55.33 ± 22.9	< 0.02
M.T.	63.29 ± 17.9	55.59 ± 22.5	N.S.
L.T.	60.47 ± 16.3	48.38 ± 24.8	< 0.04
TR	59.49 ± 22.8	41.89 ± 28.2	< 0.008
PA	30.04 ± 20.3	26.96 ± 25.7	N.S.

Table 3.12 : Comparison of the percentage areas of slight, moderate, severe fibrillation, fibrocartilage formation, bone exposure and osteophyte formation in males and females in the main study group. SLIGHT - Slight Fibrillation; MODERATE - Moderate Fibrillation; SEVERE - Severe Fibrillation; F-CART - Fibrocartilage; B.E. - Bone exposure; O'P - Osteophytes

	Males n = 39	Females n = 28	p
SLIGHT	20.43 ± 11.8	23.11 ± 14.7	N.S.
MODERATE	16.86 ± 16.0	21.67 ± 16.3	< 0.01
SEVERE	2.54 ± 5.7	4.19 ± 8.4	N.S.
F-CART	0.47 ± 1.7	1.29 ± 2.8	< 0.001
B.E.	0.04 ± 3.0	0.53 ± 2.6	< 0.01
O'P	0.82 ± 3.0	2.74 ± 6.9	< 0.001

differences were least marked in the patella and medial tibia where there were no significant differences between males and females except that the articular surface area was significantly greater in males (Table 3.13).

3.2.2 Right versus Left Comparisons

Although within the main study group right-sided knees had a significantly greater percentage areas of bone exposure and osteophytes, these differences were not significant in any region alone, and no other right - left differences were noted (see Table 3.14).

3.2.3 Cartilage Parameters

Intact Cartilage

A significantly smaller percentage area of intact cartilage was present in the patella than in other regions of the knee (Table 3.15). The lateral femoral condyle was found to have a significantly greater percentage area of intact cartilage than the trochlea in the main study group and in males (Tables 3.15 and 3.16), but no such difference occured in females (Table 3.17)

A significant negative correlation between age and the mean percentage area of intact cartilage was seen in the main study group (Figure 3.14) and this remained significant in both male and female subgroups (Figure 3.15). The correlation was found to be significant in all regions of the knee (Figures 3.16-3.18).

Slight Fibrillation

In the main study group and in males the patella had a greater percentage area of slight fibrillation than all other regions of the knee (Table 3.18 and 3.19). In females there were no significant differences between the patella and the other regions except the trochlea (Tables 3.20).

Table 3.13 : Difference between males and females for the percentage area of the various forms of cartilage change, and articular areas, within the six regions of the knee. Asterisks indicate a significant difference p < 0.05.

Variable	MF	LF	MT	LT	TR	PA	MSG
AREA mm^2	*	*	*	*	*	*	*
INTACT	*	*	-	*	*	-	*
SLIGHT	*	-	-	-	-	-	-
MODERATE	*	-	-	-	-	-	*
SEVERE	-	-	-	-	-	-	-
F'CART	*	-	-	*	*	-	*
B.E.	-	-	-	-	-	-	-
O.P	*	*	-	-	-	-	*

Table 3.14 : Comparison of the total surface area (mm2) and the percent areas of the various forms of cartilage damage seen in right and left sided knees. Values given as mean + standard deviation.

	Right n = 33	Left n = 34	p
AREA	1792.42 ± 534.8	1762.79 ± 530.6	NS
INTACT	51.86 ± 20.7	54.94 ± 17.8	NS
SLIGHT	21.17 ± 13.0	21.92 ± 13.3	NS
MODERATE	19.28 ± 16.3	18.47 ± 16.2	NS
SEVERE	3.88 ± 8.0	2.59 ± 5.8	NS
F'CART	0.88 ± 2.4	0.75 ± 2.2	NS
B.E.	0.44 ± 2.4	0.06 ± 0.5	<0.001
O.P.	2.14 ± 5.6	1.12 ± 4.4	< 0.02

MF - Medial Femur; LF - Lateral Femur; MT - Medial Tibia; LT - Lateral Tibia; TR - Trochlea; PA - Patella;
F'cart - Fibrocartilage; BE - Bone Exposure; OP - Osteophytes

Table 3.15 : The percentage area of intact cartilage within the six regions of the knee.

Multiple Wilcoxon rank tests :

Patella has significantly smaller area of intact cartilage than all other areas .
There are no other significant differences.

Table 3.16 : The percentage area of intact cartilage within the six regions of the knee in males.

Multiple Wilcoxon rank tests :

Patella has significantly smaller area of intact cartilage. other areas $0.0001 < p < 0.03$.
There are no other significant differences.

Table 3.17 : The percentage area of intact cartilage in the six regions of the knee in females.

Multiple Wilcoxon rank tests : Patella has significantly greater area of slight fibrillation than the lateral tibial plateau. There are no other significant differences.

MF - Medial Femur LF - Lateral Femur
MT - Medial Tibia LT - Lateral Tibia
TR - Trochlea PA - Patella

Table 3.15

Region	Min	25%ile	Median	75%ile	Max
MF	0	48.1	65.6	76.3	93.8
LF	0	49.6	63.3	80.9	95.4
MT	7.6	49.6	62.3	75.9	96.2
LT	0	45.7	57.0	70.6	97.7
TR	0	37.4	56.2	71.1	92.9
PA	0	15.0	26.8	46.4	95.7

Table 3.16

Region	Min	25%ile	Median	75%ile	Max
MF	1.5	59.1	68.9	82.8	91.7
LF	2.6	55.8	69.1	83.1	95.4
MT	16.9	51.8	65.7	77.8	94.8
LT	22.3	50.0	60.6	72.7	85.9
TR	3.15	52.4	59.8	76.8	92.9
PA	0	17.6	31.6	46.4	67.9

Table 3.17

Region	Min	25%ile	Median	75%ile	Max
MF	0	48.1	65.6	76.3	93.8
LF	0	49.6	63.2	80.9	95.4
MT	7.6	49.6	62.3	75.9	96.2
LT	0	45.7	57.0	70.6	97.7
TR	0	37.4	56.2	71.1	92.9
PA	0	15.0	26.8	46.4	95.7

Figure 3.14 : Graph of age in years versus the mean percent area of intact cartilage.

$$n = 67, r = -0.6640, p < 0.0001$$

% Intact Cartilage = 95.56 - 0.69 Age

Figure 3.15 : Graph of age in years versus the mean percent area of intact cartilage in males and females.

Males : $n = 39, r = -0.6319, p < 0.0001$

% Intact cartilage = 91.84 - 0.59 Age

Females : $n = 33, r = -0.6464, p < 0.0001$

% Intact cartilage = 91.98 - 0.75 Age
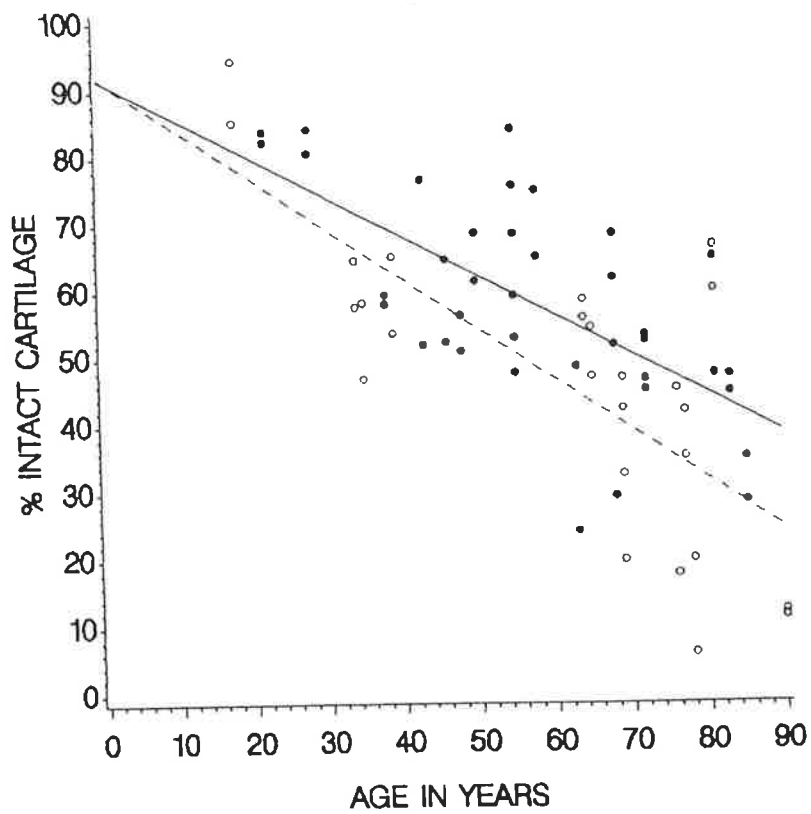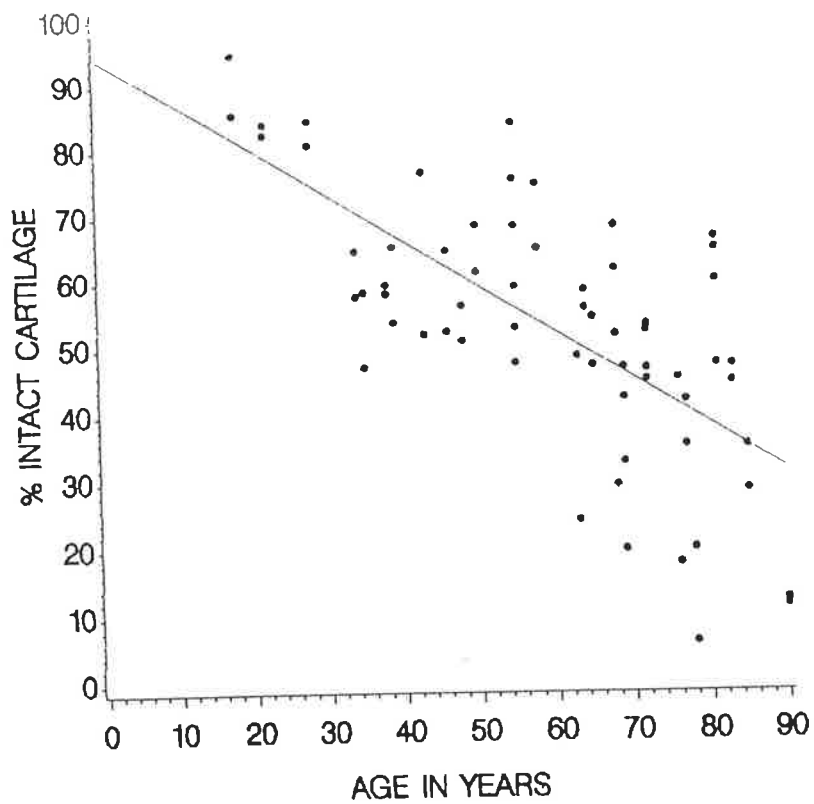
Figure 3.16 : Graph of the age in years versus the mean percent area of intact cartilage in each case for medial and lateral femoral condyles.

● —   Medial Femur : n = 67 , r = - 0.6149 , p < 0.0001

% Intact cartilage = $103.79 - 0.75$ Age

△ – —   Lateral Femur : n = 67 , r = - 0.3970 , p < 0.0005

% Intact cartilage = $89.83 - 0.45$ Age

Figure 3.17 : Graph of the age in years versus the mean percent area of intact cartilage in each case, medial and lateral tibial plateaux.

□ — ∙ —   Medial Tibia : n = 67 , r = - 0.6239 , p < 0.0001

% Intact cartilage = $100.33 - 0.68$ Age

+ — ∙ — ∙   Lateral Tibia : n = 67 , r = - 0.4816 , p < 0.0001

% Intact cartilage = $90.56 - 0.60$ Age

Figure 3.18 : Graph of the age in years versus the mean percent area of intact cartilage in each case for the trochlea and patella.

○ — —   Trochlea : n = 67 , r = - 0.6307 , p < 0.0001

% Intact cartilage = $102.03 - 0.85$ Age

✳ ∙∙∙∙∙   Patella : n = 67 , r = - 0.6868 , p < 0.0001

% Intact cartilage = $78.24 - 0.84$ Age
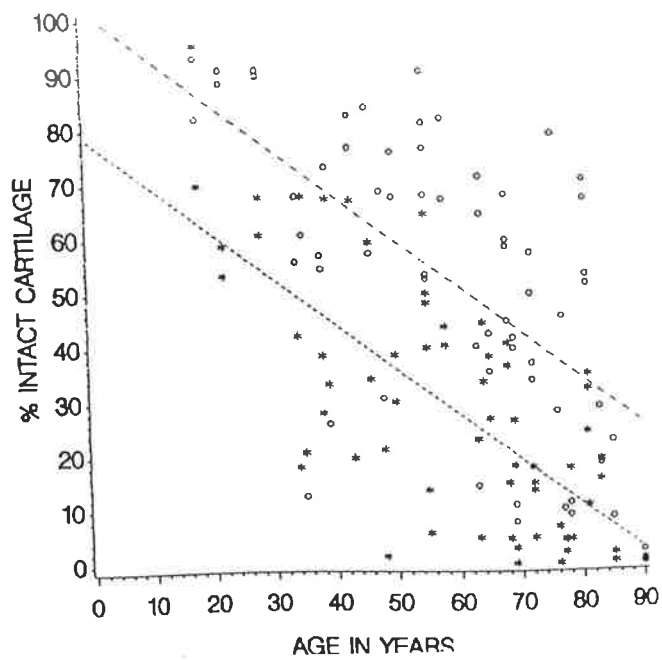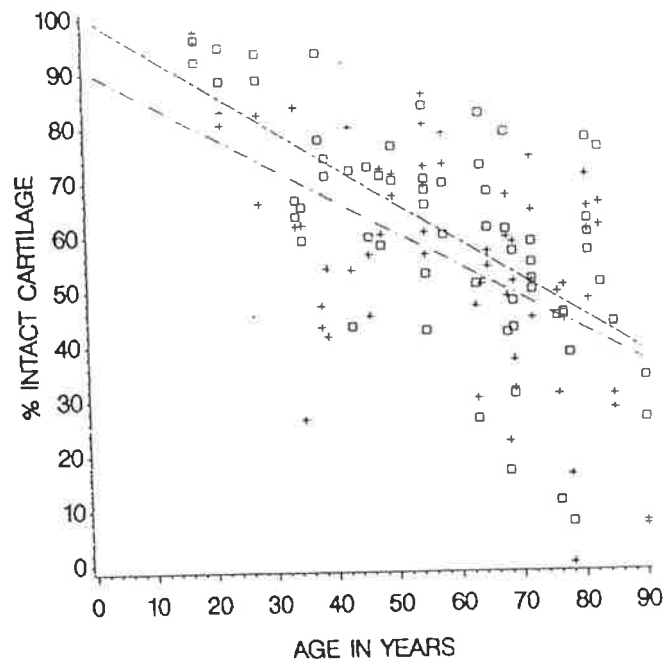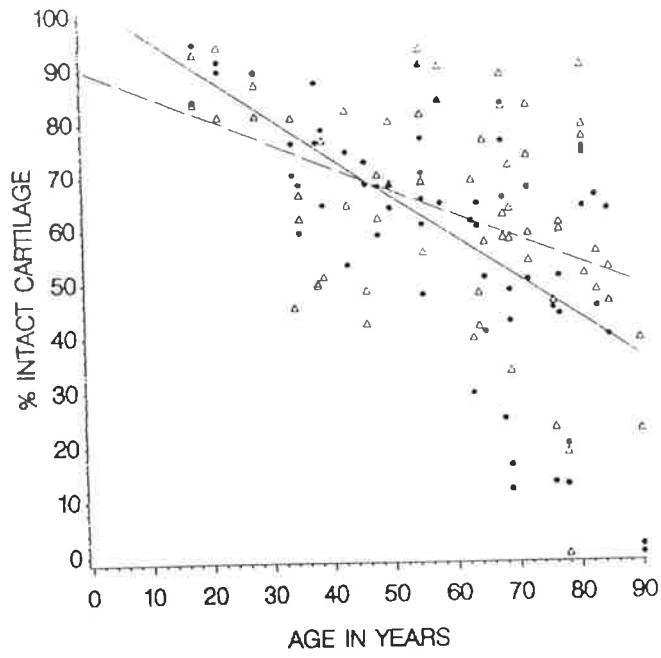
Table 3.18 : The percentage area of slight fibrillation within the six regions of the knee.

Multiple Wilcoxon rank tests :

The patella has a significantly greater area of slight fibrillation than all other regions $0.0001 < p < 0.03$.
There are no other significant differences.

Table 3.19 : The percentage area of slight fibrillation within the six regions of the knee in males.

Multiple Wilcoxon rank tests :

The patella has a significantly greater area of slight fibrillation than all other regions $0.0007 < p < 0.05$.
There are no other significant differences.

Table 3.20 : The percentage area of slight fibrillation in the six regions of the knee in females.

Multiple Wilcoxon rank tests :
The patella and trochlea have significantly greater areas of slight fibrillation than the lateral tibial plateau ($p < 0.05$).
There are no other significant differences.

MF - Medial Femur   LF - Lateral Femur
MT - Medial Tibia   LT - Lateral Tibia
TR - Trochlea   PA - Patella

Table 3.18

Region	Min	25%ile	Median	75%ile	Max
MF	1.3	9.9	17.9	26.7	56.7
LF	0	11.3	19.6	30.9	80.9
MT	3.8	8.7	20.4	28.0	50.5
LT	0	11.2	16.2	24.3	38.7
TR	4.5	11.6	18.6	28.2	81.8
PA	0	16.6	24.8	36.3	61.7

Table 3.19

Region	Min	25%ile	Median	75%ile	Max
MF	1.3	9.1	15.6	22.8	36.6
LF	2.1	10.6	19.0	30.1	80.9
MT	4.3	13.0	20.6	29.8	50.5
LT	4.1	11.6	16.2	24.3	35.5
TR	6.7	11.6	17.0	26.0	62.0
PA	4.6	17.7	24.8	35.8	55.2

Table 3.20

Region	Min	25%ile	Median	75%ile	Max
MF	4.0	14.3	20.5	31.8	56.7
LF	0	15.5	20.7	33.6	51.6
MT	3.8	8.3	19.6	25.9	47.6
LT	0	9.2	17.1	25.1	38.7
TR	4.5	13.9	24.3	37.0	81.8
PA	0	15.4	24.4	37.7	61.7

A significant positive correlation was found between age and the mean percentage area of slight fibrillation in the main study group (Figure 3.19). Although this was significant in the male subgroup (Figure 3.20), it was not significant in females. The regional correlation was significant only in the medial femoral condyle ($p < 0.002$, $r = 0.3974$, $n = 67$).

The mean percentage area of slight fibrillation exhibited a significant correlation with the mean percentage area of fibrocartilage in the main study group (Figure 3.21), but did not exhibit a significant correlation with any other cartilage parameter.

Moderate Fibrillation

Moderate fibrillation occurred over a significantly greater percentage area in the patella compared to other regions in the main study group (Table 3.21) and this was also the case in the male subgroup (Table 3.22). In females, the percent area of moderate fibrillation was significantly greater in the patella than in the medial tibia and both the medial and lateral femur (Table 3.23). In males and the total study group the percentage area of moderate fibrillation was significantly greater in the trochlea and lateral tibial plateau than the lateral femoral condyle (Tables 3.21 and 3.22).

A significant non-linear correlation was found between age and the mean percentage area of moderate fibrillation (Figure 3.22) and this was significant in both male and female subgroups (Figure 3.23). The correlation was significant in all regions of the knee (Figures 3.24-3.26).

The mean percentage area of moderate fibrillation exhibited significant positive correlations with the mean percentage area of severe fibrillation (Figure 3.27), fibrocartilage ($p < 0.001$, $r = 0.4514$, $n = 67$) and bone exposure ($p < 0.005$, $r = 0.5084$, $n = 67$).

Figure 3.19 : Graph of age in years versus the mean percent area of slight fibrillation

$n = 67$, $r = 0.2258$, $p < 0.001$

% Slight fibrillation $= 12.16 + 0.16$ Age

Figure 3.20 : Graph of age in years versus the mean percent area of slight fibrillation in males and females.

● —   Males : $n = 39$, $r = 0.4813$, $p < 0.001$

% Slight fibrillation $= 9.22 + 0.19$ Age

Females : $n = 33$, $r = 0.2580$, Not significant

% Slight fibrillation $= 16.22 + 0.11$ Age

Figure 3.21 : Graph of mean percent area of slight fibrillation versus the mean percent area of fibrocartilage.

$n = 67$, $r = 0.2580$, $p < 0.05$

% Fibrocartilage $= 0.40 + 0.02$ % Slight Fibrillation
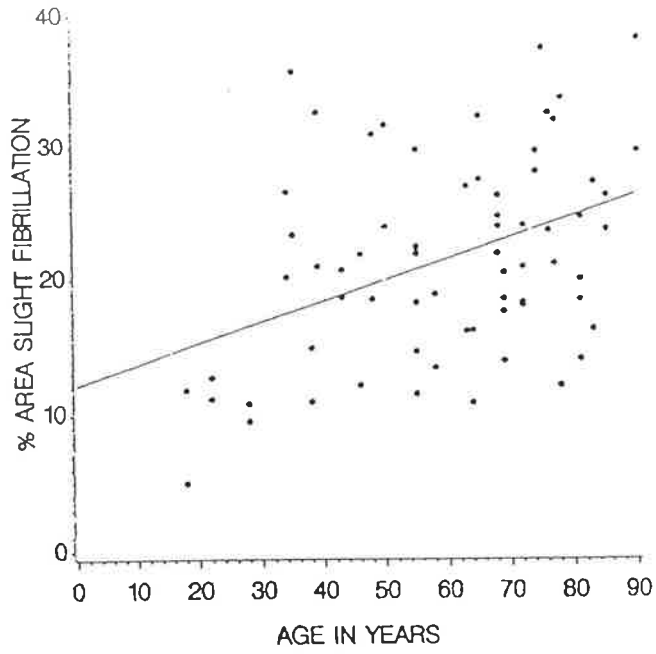
Table 3.21 : The percentage area of moderate fibrillation within the six regions of the knee.

Multiple Wilcoxon rank tests :

The patella has a significantly greater area of moderate fibrillation than all other regions p < 0.0001
The lateral tibia has significantly greater areas of moderate fibrillation than the medial and lateral femoral condyles p < 0.02 and p < 0.0013 respectively.
The trochlea has significantly greater area of moderate fibrillation than the lateral femur p < 0.02.

Table 3.22 : The percentage area of moderate fibrillation within the six regions of the knee in males.

Multiple Wilcoxon rank tests :

The patella has significantly greater area of moderate fibrillation than all other regions p < 0.0001.
The lateral tibia has significantly greater areas of moderate fibrillation than either the medial or lateral femoral condyles, p < 0.05 and p < 0.005 respectively.
The trochlea also has a signifiantly greater area of moderate fibrillation than the lateral condyle (p < 0.05).

Table 3.23 : The percentage area of moderate fibrillation in the six regions of the knee in females.

Multiple Wilcoxon rank tests :

The patella has a significantly greater area of moderate fibrillation than the medial tibial plateau and the medial and lateral femoral condyles (p < 0.004 in all cases).
There are no other significant differences.

MF - Medial Femur LF - Lateral Femur
MT - Medial Tibia   LT - Lateral Tibia
TR - Trochlea   PA - Patella

Table 3.21

Region	Min	25%ile	Median	75%ile	Max
MF	0	5.0	10.6	18.9	60.0
LF	0	1.9	7.3	18.1	48.6
MT	0	3.0	12.4	24.9	41.9
LT	0	8.4	17.0	28.7	49.6
TR	0	5.6	14.6	30.7	63.7
PA	0	21.3	33.4	46.8	82.7

Table 3.22

Region	Min	25%ile	Median	75%ile	Max
MF	0	4.1	7.8	16.3	60.0
LF	0	1.9	5.4	15.0	40.6
MT	0	1.9	7.4	24.0	41.3
LT	0	5.9	14.5	23.7	49.6
TR	0	3.4	12.4	27.5	57.0
PA	0	21.3	35.3	44.5	75.7

Table 3.23

Region	Min	25%ile	Median	75%ile	Max
MF	0	8.3	14.1	23.8	39.1
LF	0	2.2	13.2	28.3	48.6
MT	0	11.3	17.4	26.9	41.9
LT	0	11.1	24.0	33.5	48.1
TR	0	6.3	18.6	34.7	63.7
PA	0	19.1	29.3	47.6	82.7

Figure 3.22 : Graph of the age in years versus the mean percent area of moderate fibrillation in each case.

$$n = 67 , r = 0.6626 , p < 0.0001$$

$$\% \text{ Moderate fibrillation} = 5.56 \, e^{\,0.02 \text{ Age}}$$

Figure 3.23 : Graph of the age in years versus the mean percent area of moderate fibrillation in each case for males and females.

● —— Males : $n = 39 , r = 0.6076 , p < 0.001$

$$\% \text{ Moderate fibrillation} = 5.17 \, e^{\,0.02 \text{ Age}}$$

○ – – – Females : $n = 28 , r = 0.5694 , p < 0.0001$

$$\% \text{ Moderate fibrillation} = 6.89 \, e^{\,0.02 \text{ Age}}$$

Figure 3.24 : Graph of the age in years versus the mean percent area of moderate fibrillation in each case for medial and lateral femoral condyles.

● —— Medial Femur : $n = 67 , r = 0.4953 , p < 0.0001$

$$\% \text{ Moderate fibrillation} = 3.44 \, e^{\,0.02 \text{ Age}}$$

Δ – – – Lateral Femur : $n = 67 , r = 0.3116 , p < 0.01$

$$\% \text{ Moderate fibrillation} = 3.22 \, e^{\,0.02 \text{ Age}}$$
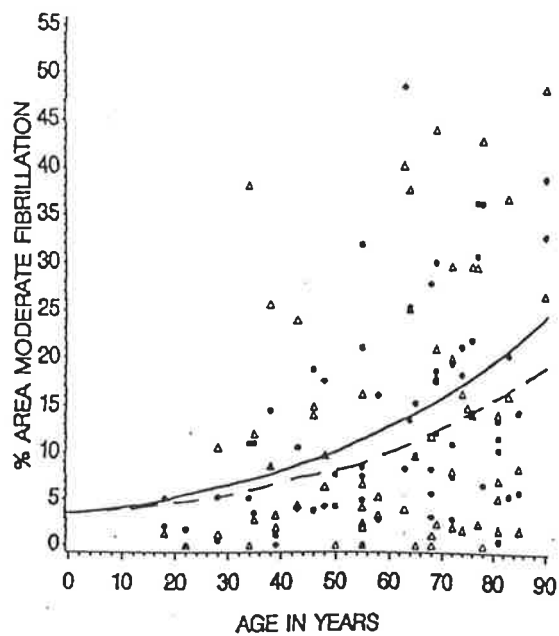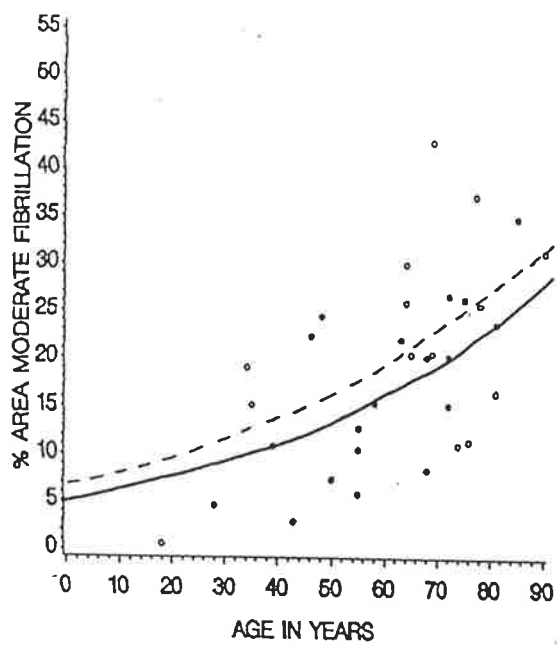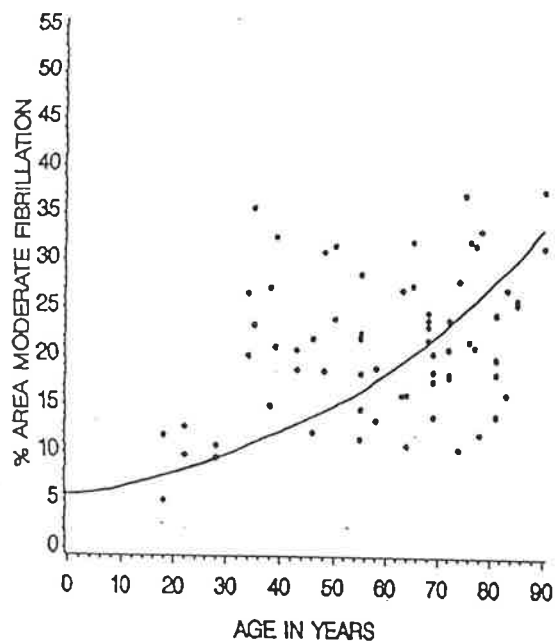
Figure 3.25 : Graph of the age in years versus the mean percent area of moderate fibrillation in each case, medial and lateral tibial plateaux.

◻ — - —   Medial Tibia : n = 67 , r = 0.5421 , p < 0.0001

$\%$ Moderate fibrillation $= 3.15\ e^{0.02\ Age}$

+ —·—·   Lateral Tibia : n = 67 , r = 0.5490 , p < 0.0001

$\%$ Moderate fibrillation $= 5.08\ e^{0.02\ Age}$

Figure 3.26 : Graph of the age in years versus the mean percent area of moderate fibrillation in each case for the trochlea and patella.

○ — —   Trochlea : n = 67 , r = 0.5656 , p < 0.0001

$\%$ Moderate fibrillation $= 3.73\ e^{0.03\ Age}$

✳ - - - -   Patella : n = 67 , r = 0.4328 , p < 0.001

$\%$ Moderate fibrillation $= 16.8\ e^{0.01\ Age}$

Figure 3.27 : Graph of the mean percent area of moderate fibrillation versus the mean percent area of severe fibrillation in each case.

n = 67 , r = 0.6165 , p < 0.0001

Severe Fibrillation = -0.58 + 0.20 Moderate Fibrillation
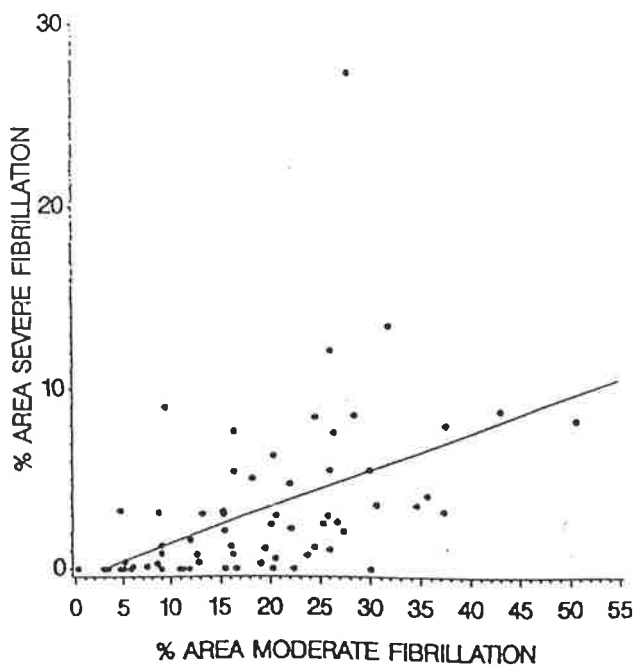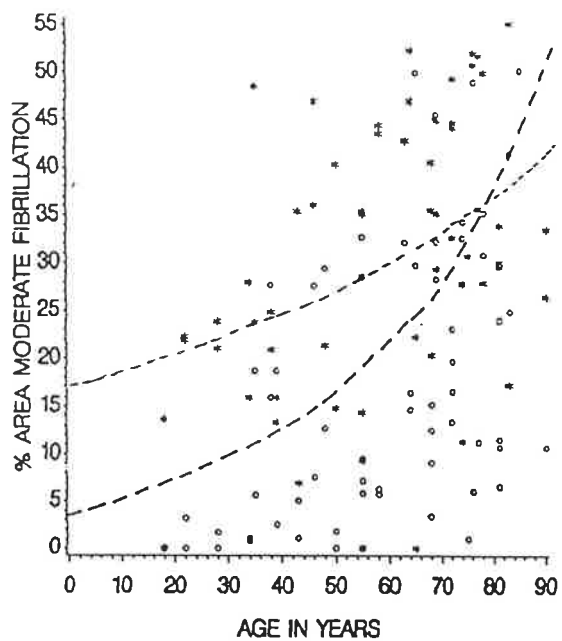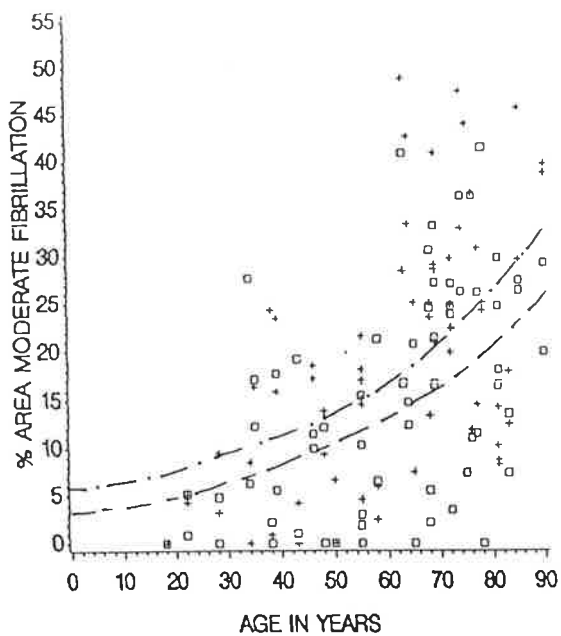
Severe Fibrillation

The percentage area of severe fibrillation was significantly greater in the patella than all other regions except the lateral tibial plateau and medial femoral condyle in the main study group and in females (Tables 3.24 and 3.26). In males there was a significantly greater percentage area of severe fibrillation in the patella than in the medial tibia or lateral femur only (Tables 3.25). The percentage area of severe fibrillation was significantly lower in the lateral femoral condyle than in all other regions except the medial tibial plateau in all groups (Tables 3.24 - 3.26).

Age and the mean percentage area of severe fibrillation exhibited a significant positive non-linear correlation in the main study group (Figure 3.28), and in both males and females (Figure 3.29). The correlation was significant in all regions of the knee except the lateral femoral condyle and lateral tibial plateau (Figures 3.30 and 3.31).

The mean percentage area of severe fibrillation in the main study group correlated significantly with the mean percentage area of fibrocartilage (Figure 3.32), bone exposure (p < 0.002, r = 0.3865, n = 67) and osteophytes (p < 0.0001, r = 0.5728, n = 67).

Fibrocartilage

The percentage area of fibrocartilage in the main study group was significantly greater in the patella than in all other areas except the lateral tibial plateau, which, in turn, was significantly greater than the remaining regions of the knee (Table 3.27). In both males and females, the patella had a significantly greater percentage area of fibrocartilage than the medial tibial plateau (Table 3.28 and 3.29). In females, the patella and lateral tibial plateau had significantly more fibrocartilage than the medial femoral condyle, and the trochlea had a greater area of fibrocartilage than either the lateral femur or medial tibia (Table 3.29. In males, the percentage area of fibrocartilage in the patella and lateral tibial plateau was significantly greater than in the medial femur (Table 3.28).

Table 3.24 : The percentage area of severe fibrillation within the six regions of the knee.

Multiple Wilcoxon rank tests :

The percent area of severe fibrillation in the lateral femur is significantly less than in all other regions except the medial tibia ($p < 0.0004$ in all cases).
The medial tibia has significantly less percent area of severe fibrillation than all other regions except the lateral tibia ($p < 0.05$).
The patella has significantly greater percent area of severe fibrillation than all other regions except the medial femur and lateral tibia ($p < 0.05$).

Table 3.25 : The percentage area of severe fibrillation within the six regions of the knee in males.

Multiple Wilcoxon rank tests :

The lateral femur has significantly smaller area of severe fibrillation than all other regions except the medial tibia ($p < 0.0008$ in all cases).
The medial tibia has a significantly smaller area of severe fibrillation than all other regions ($p < 0.02$ in all cases).

Table 3.26 : The percentage area of severe fibrillation within the six regions of the knee in females.

Multiple Wilcoxon rank tests :

The lateral femur has significantly smaller area of severe fibrillation than all other regions except the trochlea and medial tibia ($p < 0.02$ in all cases)
The medial tibia has significantly smaller area of severe fibrillation than either the lateral tibia or patella ($p < 0.03$).
The patella has significantly greater area of severe fibrillation than all other regions except the medial femur and lateral tibia ($p < 0.05$)

MF - Medial Femur   LF - Lateral Femur
MT - Medial Tibia   LT - Lateral Tibia
TR - Trochlea   PA - Patella

Table 3.24

Region	Min	25%ile	Median	75%ile	Max
MF	0	0	0.6	4.6	30.8
LF	0	0	0	0	52.8
MT	0	0	0	0	15.1
LT	0	0	0	6.2	36.4
TR	0	0	0	2.2	37.2
PA	0	0	1.2	9.6	43.9

Table 3.25

Region	Min	25%ile	Median	75%ile	Max
MF	0	0	0	4.7	18.7
LF	0	0	0	0	2.1
MT	0	0	0	0	12.3
LT	0	0	0	5.9	21.9
TR	0	0	0	2.2	37.2
PA	0	0	0	5.4	34.5

Table 3.26

Region	Min	25%ile	Median	75%ile	Max
MF	0	0	1.8	4.3	30.8
LF	0	0	0	0	52.8
MT	0	0	0	1.5	15.1
LT	0	0	2.9	6.7	36.4
TR	0	0	0	5.8	31.8
PA	0	0	3.0	11.8	43.9

Figure 3.28 : Graph of the age in years versus the mean percent area of severe fibrillation in each case.

$$n = 67 \ , \ r = 0.5430 \ , \ p < 0.001$$

$$\% \ \text{Severe fibrillation} = 0.26 \ e^{0.04 \ \text{Age}}$$

Figure 3.29 : Graph of the age in years versus the mean percent area of severe fibrillation in each case for males and females.

● —— Males : $n = 39 \ , \ r = 0.4950 \ , \ p < 0.01$

$$\% \ \text{Severe fibrillation} = 0.27 \ e^{0.04 \ \text{Age}}$$

○ — — Females : $n = 28 \ , \ r = 0.5268 \ , \ p < 0.05$

$$\% \ \text{Severe fibrillation} = 0.36 \ e^{0.04 \ \text{Age}}$$

Figure 3.30 : Graph of the age in years versus the mean percent area of severe fibrillation in each case for the tibiofemoral joint.

● —— Medial Femur : $n = 67 \ , \ r = 0.4619 \ , \ p < 0.01$

$$\% \ \text{Severe fibrillation} = 0.63 \ e^{0.03 \ \text{Age}}$$

Lateral Femur : $n = 67 \ , \ r = 0.1642 \ , \ \text{Not Significant}$

$$\% \ \text{Severe fibrillation} = 0.01 \ e^{0.07 \ \text{Age}}$$

□ — - — Medial Tibia : $n = 67 \ , \ r = 0.2846 \ , \ p < 0.02$

$$\% \ \text{Severe fibrillation} = 0.001 \ e^{0.01 \ \text{Age}}$$

Lateral Tibia : $n = 67 \ , \ r = 0.2395 \ , \ \text{Not Significant}$

$$\% \ \text{Severe fibrillation} = 0.66 \ e^{0.03 \ \text{Age}}$$
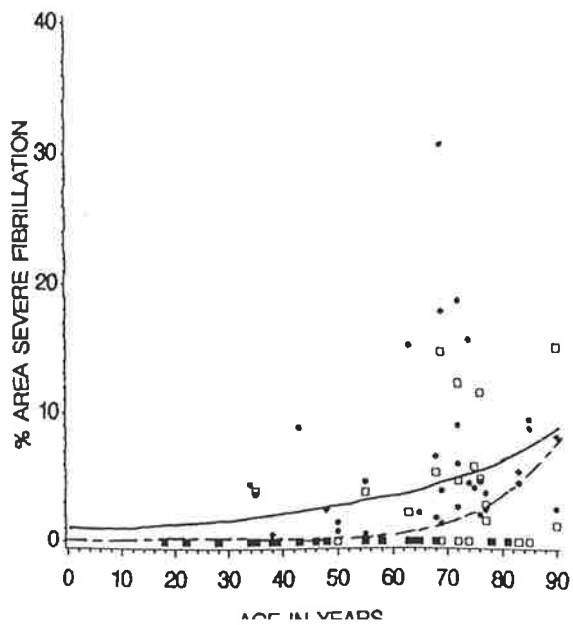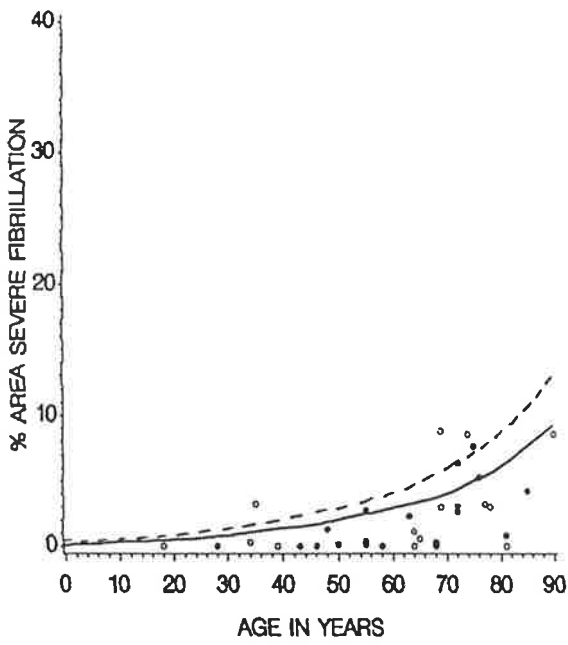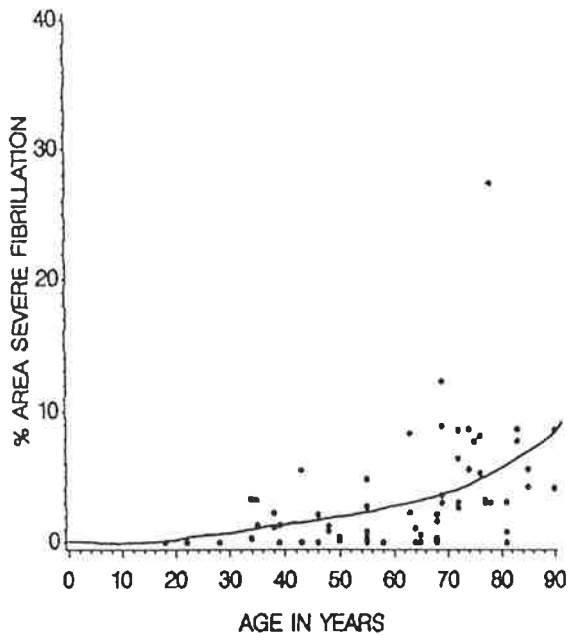
Figure 3.31 : Graph of the age in years versus the mean percent area of severe fibrillation in each case for the trochlea and patella.

o — — Trochlea : n = 67 , r = 0.3374 , p < 0.01

$$\% \text{ Severe fibrillation} = 0.28 \, e^{\,0.04 \, \text{Age}}$$

✳ - - - - Patella : n = 67 , r = 0.4822 , p < 0.005

$$\% \text{ Severe fibrillation} = 0.17 \, e^{\,0.05 \, \text{Age}}$$

Figure 3.32 : Graph of the mean percent area of severe fibrillation versus the mean percent area of fibrocartilage in each case.

n = 67 , r = 0.4541 , p < 0.0001

Fibrocartilage = - 0.03 + 0.05 Severe Fibrillation.
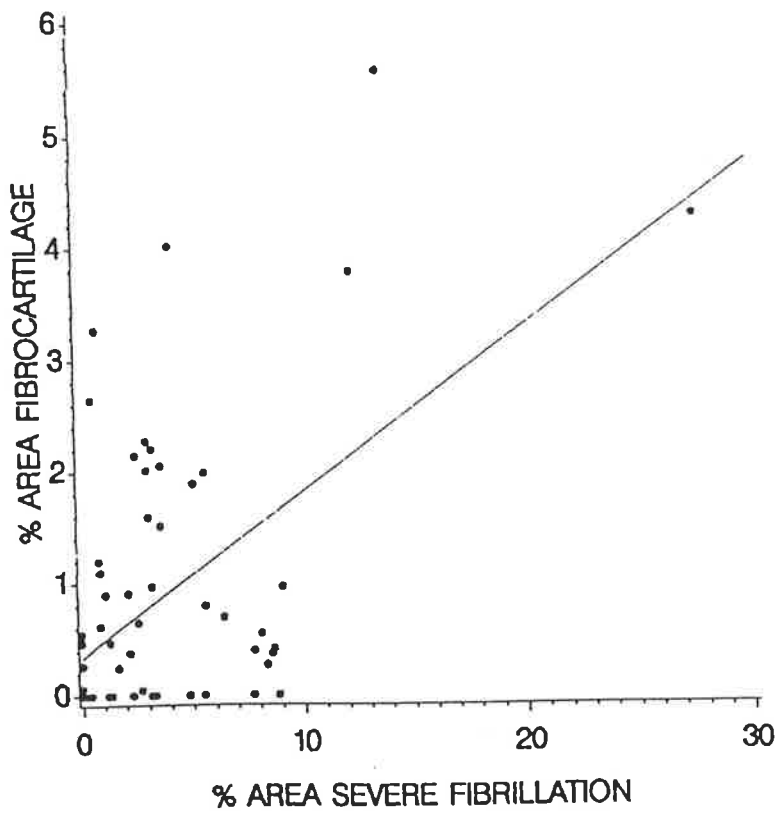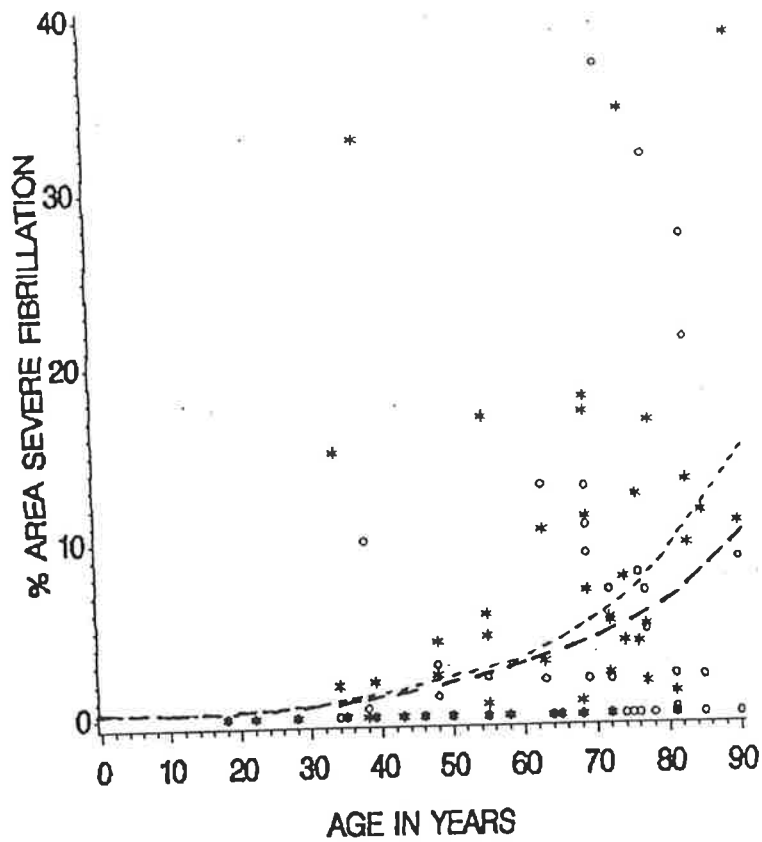
Table 3.27 : The percentage area of fibrocartilage within the six regions of the knee.

Multiple Wilcoxon rank tests :

The patella has significantly greater percent area of fibrocartilage than all other regions except the lateral tibia ($p < 0.02$ in all cases).
The lateral tibia has significantly greater percent area of fibrocartilage than all other regions except the patella ($p < 0.005$).
The only other significant difference is between the medial tibia and both the medial femur and trochlea ($p < 0.03$).

Table 3.28 : The percentage area of fibrocartilage within the six regions of the knee in males.

Multiple Wilcoxon rank tests :

Both the patella and lateral tibia have significantly greater areas of fibrocartilage than either the medial femur or tibia ($p < 0.03$)
The medial tibia has a significantly greater area of fibrocartilage than the lateral femur ($p < 0.05$).

Table 3.29 : The percentage area of fibrocartilage in the six regions of the knee in females.

Multiple Wilcoxon rank tests :
The patella, trochlea and lateral tibia have significantly greater areas of fibrocartilage than either the lateral femur or medial tibia ($p < 0.005$)

MF - Medial Femur   LF - Lateral Femur
MT - Medial Tibia   LT - Lateral Tibia
TR - Trochlea   PA - Patella

Table 3.27

Region	Min	25%ile	Median	75%ile	Max
MF	0	0	0	0	11.7
LF	0	0	0	0	5.5
MT	0	0	0	0	3.0
LT	0	0	0	2.8	8.7
TR	0	0	0	0	6.6
PA	0	0	0	2.8	16.3

Table 3.28

Region	Min	25%ile	Median	75%ile	Max
MF	0	0	0	4.7	18.7
LF	0	0	0	0	2.1
MT	0	0	0	0	12.3
LT	0	0	0	5.9	21.9
TR	0	0	0	2.2	37.2
PA	0	0	0	5.4	34.5

Table 3.29

Region	Min	25%ile	Median	75%ile	Max
MF	0	0	0	0.5	11.7
LF	0	0	0	0	3.9
MT	0	0	0	0	3.0
LT	0	0	0.5	3.8	8.7
TR	0	0	0	1.2	6.6
PA	0	0	0	4.6	14.0

There was a significant positive non-linear correlation between age and the mean percentage area of fibrocartilage in the main study group (Figure 3.33) and this was significant in both males and females (Figure 3.34). The correlation was found to be significant in all regions of the knee except the lateral femoral condyle and medial tibial plateau (Figures 3.35 and 3.36).

The percentage area of fibrocartilage in the main study group exhibited a significant positive correlation with both the area of bone exposure ($p < 0.002$, $r = 0.3865$, $n = 67$) and osteophytes ($p < 0.0001$, $r = 0.5728$, $n = 67$).

Bone Exposure

No significant regional differences in the percentage area of bone exposure were found in the main study group or the male subgroup (Tables 3.30 and 3.31). In the female subgroup there was a significantly greater percent area in the lateral tibia as opposed to the lateral femur (Table 3.32).

A significant positive correlation was found between age and the percentage area of bone exposure, which was significant in females but not males, and regionally was significant in all regions except for the trochlea and the lateral femoral condyle (Table 3.33).

The percentage area of bone exposure correlated significantly with the percentage area of osteophyte in the main study group ($n = 67$, $r = 0.4768$, $p < 0.0001$).

Osteophytes

In the main study group the percentage area of osteophyte was significantly smaller in the patella compared to all other regions (Table 3.34). Significant differences in the percentage area of osteophytes were found only between the patella and the medial and lateral tibial plateaux in males, whilst in females the area was significantly greater in all regions compared to the trochlea or the patella (Table 3.35 and 3.36).

Figure 3.33 : Graph of the age in years versus the mean percent area of fibrocartilage in each case.

$n = 67$, $r = 0.6283$, $p < 0.0001$

% Fibrocartilage $= 5 \times 10^{-4} \, e^{0.1 \, Age}$

Figure 3.34 : Graph of the age in years versus the mean percent area of fibrocartilage in each case for males and females.

● —— Males : $n = 39$, $r = 0.5068$, $p < 0.002$

% Fibrocartilage $= 4 \times 10^{-4} \, e^{0.1 \, Age}$

○ – – – Females : $n = 28$, $r = 0.6155$, $p < 0.001$

% Fibrocartilage $= 6 \times 10^{-4} \, e^{0.1 \, Age}$
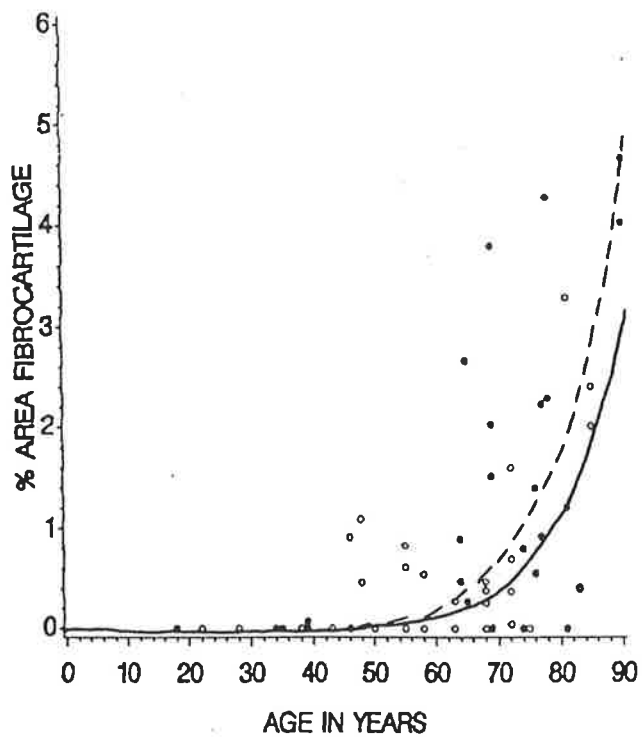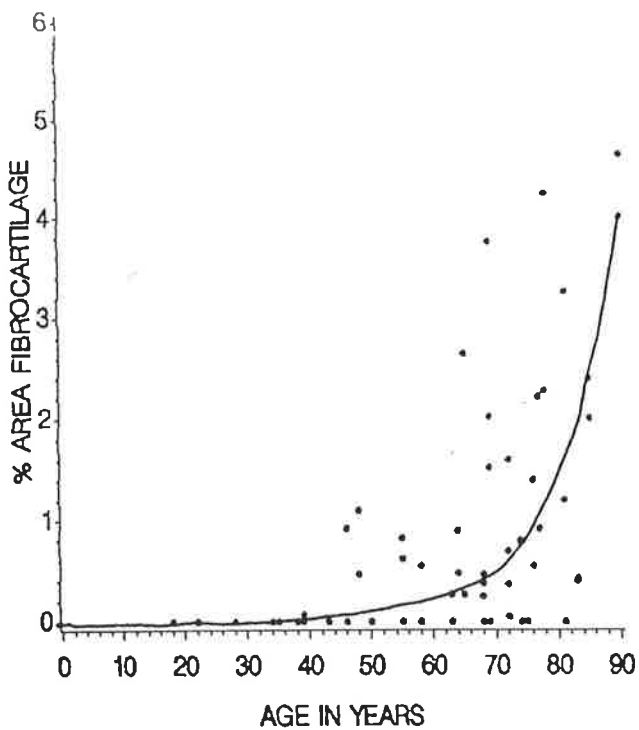
Figure 3.35 : Graph of the age in years versus the mean percent area of fibrocartilage in each case for the tibiofemoral joint.

● —   Medial Femur : n = 67 , r = 0.3494 , p < 0.004

$$\% \text{ Fibrocartilage} = 6 \times 10^{-4} \, e^{0.1 \, \text{Age}}$$

Lateral Femur : n = 67 , r = 0.2582 , Not Significant

$$\% \text{ Fibrocartilage} = 1 \times 10^{-4} \, e^{0.1 \, \text{Age}}$$

Medial Tibia : n = 67 , r = 0.1308 , Not Significant

$$\% \text{ Fibrocartilage} = 2.5 \times 10^{-5} \, e^{0.1 \, \text{Age}}$$

+ —·—   Lateral Tibia : n = 67 , r = 0.4565 , p < 0.0001

$$\% \text{ Fibrocartilage} = 8 \times 10^{-4} \, e^{0.1 \, \text{Age}}$$

Figure 3.36 : Graph of the age in years versus the mean percent area of fibrocartilage in each case for the trochlea and patella.

○ — —   Trochlea : n = 67 , r = 0.3661 , p < 0.02

$$\% \text{ Fibrocartilage} = 3 \times 10^{-4} \, e^{0.10 \, \text{Age}}$$

✳ — — — —   Patella : n = 67 , r = 0.4828 , p < 0.0005

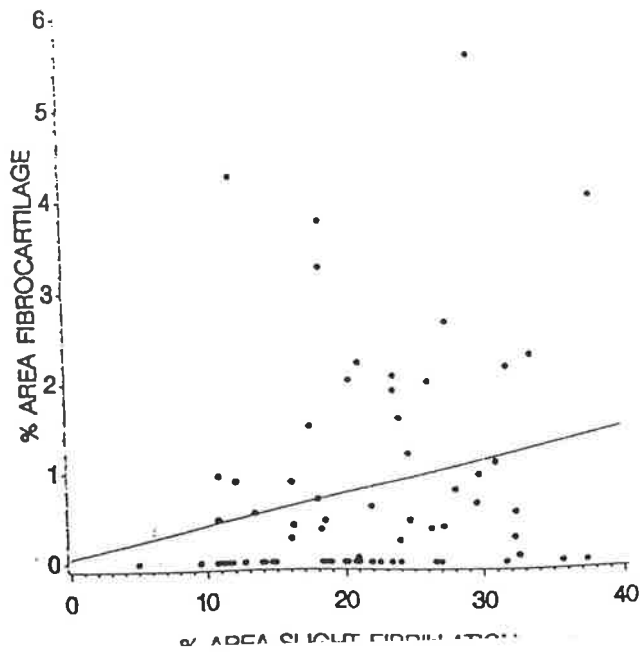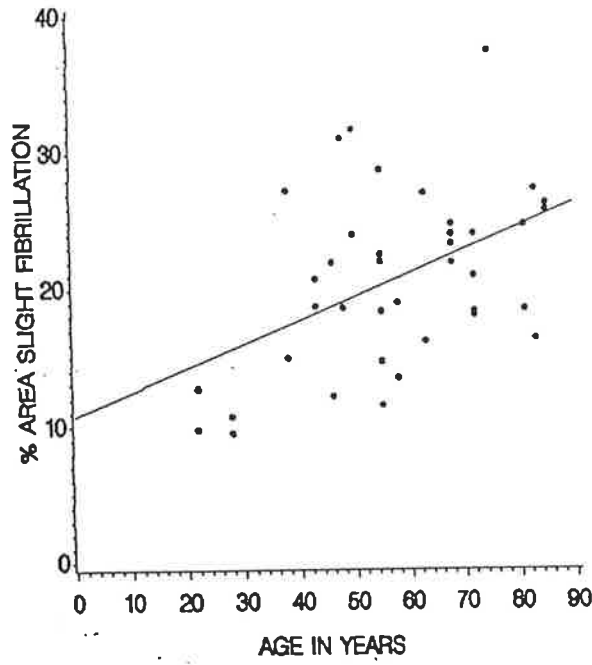$$\% \text{ Fibrocartilage} = 0.017 \, e^{0.07 \, \text{Age}}$$
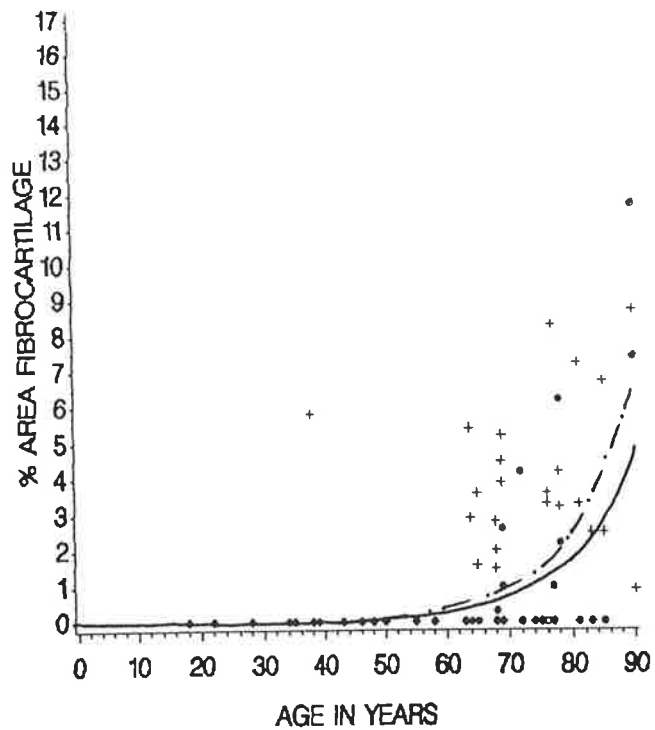
Table 3.30: The percentage area of bone exposure within the six regions of the knee.

Multiple Wilcoxon rank tests :
　　The lateral tibia has a significantly greater percent area of bone exposure than the lateral femur (p < 0.001).
　　There are no other significant regional differences.

Table 3.31 : The percentage area of bone exposure within the six regions of the knee in males.

Multiple Wilcoxon rank tests : No significant differences between any of the regions.

Table 3.32 : The percentage area of bone exposure in the six regions of the knee in females.

Multiple Wilcoxon rank tests : No significant differences between any of the regions.

MF - Medial Femur　LF - Lateral Femur
MT - Medial Tibia　　LT - Lateral Tibia
TR - Trochlea　　　　PA - Patella

Table 3.30

Region	Min	25%ile	Median	75%ile	Max
MF	0	0	0	0	27
LF	0	0	0	0	4.3
MT	0	0	0	0	4.9
LT	0	0	0	0	9.8
TR	0	0	0	0	9.7
PA	0	0	0	0	9.9

Table 3.31

Region	Min	25%ile	Median	75%ile	Max
MF	0	0	0	0	1.6
LF	0	0	0	0	0
MT	0	0	0	0	0.96
LT	0	0	0	0	0
TR	0	0	0	0	2.8
PA	0	0	0	0	3.3

Table 3.32

Region	Min	25%ile	Median	75%ile	Max
MF	0	0	0	0	27
LF	0	0	0	0	4.3
MT	0	0	0	0	4.9
LT	0	0	0	0	9.8
TR	0	0	0	0	9.7
PA	0	0	0	0	9.9

Table 3.33 : Correlation between age and the percentage areas of bone exposure
(BE) within the study group.

MT - Medial Tibia;   MF - Medial Femur;

LF - Lateral Femur; LT - Lateral Tibia;

NS - Not significant MSG - Main study group

	p	r	Regression
MSG	< 0.002	0.3724	2×10^{-4} e 0.10 Age = BE
Males	NS	0.2961	3×10^{-5} e 0.10 Age = BE
Females	< 0.009	0.4924	2×10^{-4} e 0.10 Age = BE
MF	< 0.02	0.3069	3×10^{-4} e 0.10 Age = BE
LF	NS	0.1434	3×10^{-4} e 0.10 Age = BE
MT	< 0.03	0.2820	2×10^{-4} e 0.10 Age = BE
LT	< 0.05	0.2490	8×10^{-5} e 0.10 Age = BE
Trochlea	NS	0.1092	1×10^{-4} e 0.10 Age = BE
Patella	< 0.03	0.2719	2×10^{-4} e 0.10 Age = BE

Table 3.34: The percentage area of osteophytes within the six regions of the knee.

Multiple Wilcoxon rank tests :
    The percent area of osteophytes is significantly smaller in the patella than all other regions ($p < 0.01$ in all cases)

Table 3.35: The percentage area of osteophytes within the six regions of the knee in males.

Multiple Wilcoxon rank tests :

    The area of osteophytes is significantly smaller in the patella than in the medial and lateral tibia only ($p < 0.02$ and $p < 0.008$ respectively)

Table 3.36 : The percentage area of osteophytes in the six regions of the knee in females.

Multiple Wilcoxon rank tests :

The percent area of osteophytes is significantly smaller in the patella than all other regions except the trochlea ($p < 0.05$ in all cases)

MF - Medial Femur   LF - Lateral Femur
MT - Medial Tibia   LT - Lateral Tibia
TR - Trochlea   PA - Patella

Table 3.34

Region	Min	25%ile	Median	75%ile	Max
MF	0	0	0	0	29.9
LF	0	0	0	0	22.6
MT	0	0	0	0	27.4
LT	0	0	0	0	32.0
TR	0	0	0	0	10.4
PA	0	0	0	0	2.8

Table 3.35

Region	Min	25%ile	Median	75%ile	Max
MF	0	0	0	0	21.0
LF	0	0	0	0	10.5
MT	0	0	0	0	12.9
LT	0	0	0	0	21.7
TR	0	0	0	0	10.4
PA	0	0	0	0	0

Table 3.36

Region	Min	25%ile	Median	75%ile	Max
MF	0	0	0	6.95	29.9
LF	0	0	0	2.4	22.6
MT	0	0	0	6.7	27.4
LT	0	0	0	0	32.0
TR	0	0	0	0	5.6
PA	0	0	0	0	2.8

The significant positive non-linear correlation between age and the percentage area of osteophytes (Figure 3.37) was significant in females, but not in males (Figure 3.38), and regionally was significant only in the medial femoral condyle and medial tibial plateau (Figure 3.39).

3.2.4 Inter-regional Variation

The Patellofemoral Joint

In comparing the values for the opposing surfaces within the patellofemoral joint in the main study group, it was found on paired t-testing that the percentage areas of moderate fibrillation, severe fibrillation and fibrocartilage are significantly greater, and the percentage area of intact cartilage significantly smaller in the patella than in the trochlea (Table 3.37).

In the main study group, significant positive correlations were found between the two regions for the percentage areas of all forms of cartilage change except slight fibrillation (Table 3.38).

The Tibiofemoral joint

Significant differences between the medial femoral condyle and tibial plateau were found for all cartilage parameters except for percentage areas of bone exposure and intact cartilage (Table 3.39).

Significant positive correlations were found between these two regions for the percentage areas of all forms of cartilage change except fibrocartilage formation (Table 3.40).

In the main study group, the lateral tibial plateau had significantly greater percentage areas of all forms of cartilage damage than the opposing femoral condyle, as well as significantly smaller percent area of intact cartilage (Table 3.41).

Figure 3.37 : Graph of age in years versus the mean percent area of osteophytes in each case.

$$n = 67 , r = 0.2359 , p < 0.05$$

$$\% \text{ Osteophytes} = 0.12 \, e^{0.04 \, \text{Age}}$$

Figure 3.38 : Graph of age in years versus the mean percent area of osteophytes in males and females.

Males : $n = 39, r = 0.0388$, Not significant

$$\% \text{ Osteophytes} = 0.0003 \, e^{0.10 \, \text{Age}}$$

O — — Females : $n = 33, r = 0.3611, p < 0.0001$

$$\% \text{ Osteophytes} = 0.26 \, e^{0.04 \, \text{Age}}$$

Figure 3.39 : Graph of age in years versus the mean percent area of osteophytes in each region.

● — Medial Femur : $n = 67, r = 0.3125, p < 0.01$

$$\% \text{ Osteophytes} = 0.23 \, e^{0.04 \, \text{Age}}$$

Lateral Femur : $n = 67, r = 0.1752$, Not significant

$$\% \text{ Osteophytes} = 0.31 \, e^{0.03 \, \text{Age}}$$

▯ — · — Medial Tibia : $n = 67, r = 0.4143, p < 0.001$

$$\% \text{ Osteophytes} = 0.03 \, e^{0.06 \, \text{Age}}$$

Lateral Tibia : $n = 67, r = 0.1580$, Not significant

$$\% \text{ Osteophytes} = 0.04 \, e^{0.05 \, \text{Age}}$$

Trochlea : $n = 67, r = 0.1221$, Not significant

$$\% \text{ Osteophytes} = 0.0003 \, e^{0.10 \, \text{Age}}$$

Patella : $n = 67, r = 0.0612$, Not significant

$$\% \text{ Osteophytes} = 9 \times 10^{-6} \, e^{0.10 \, \text{Age}}$$
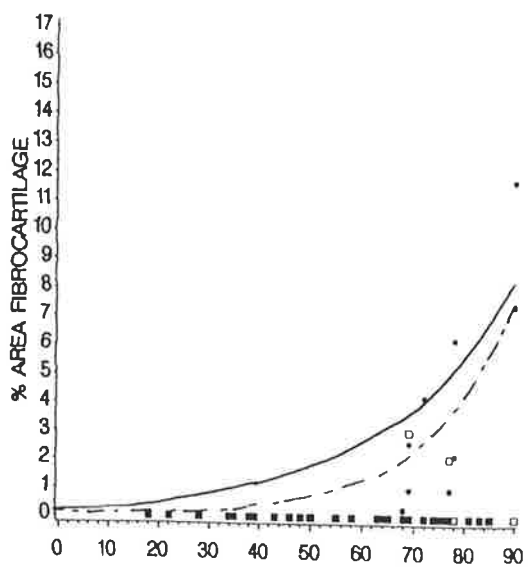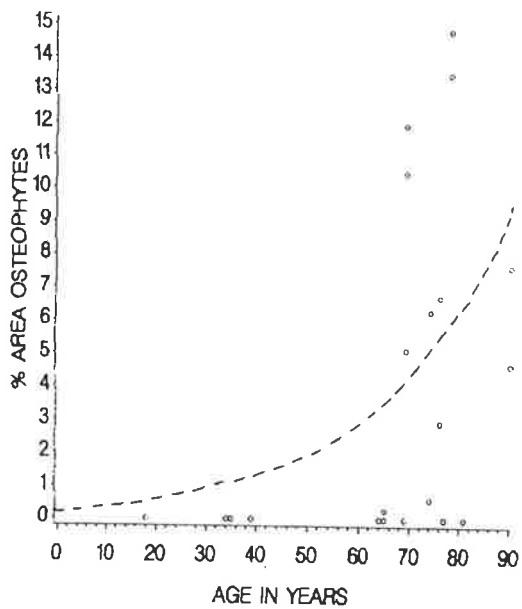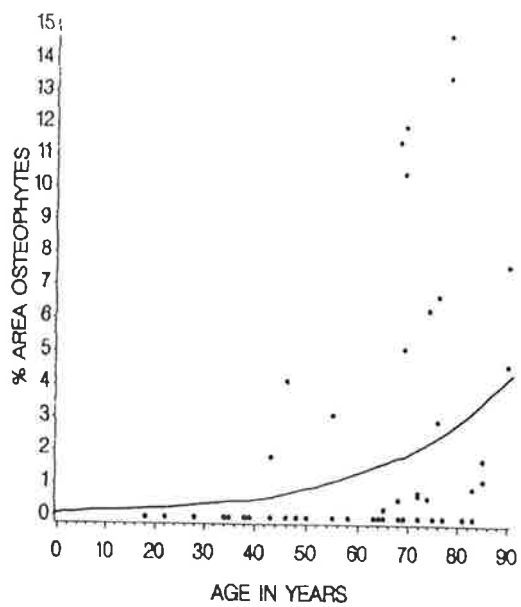
Table 3.37 : Comparison of the percent areas of the various forms of cartilage changes seen in the trochlea and patella. Values given as mean $\pm$ standard deviation. Comparison made using a paired t-test.

Variable	Trochlea	Patella	p
INTACT	52.21 $\pm$ 26.5	28.79 $\pm$ 22.7	< 0.001
SLIGHT	22.81 $\pm$ 15.4	27.06 $\pm$ 14.3	< 0.001
MODERATE	19.60 $\pm$ 18.0	33.93 $\pm$ 17.9	< 0.009
SEVERE	3.43 $\pm$ 7.5	5.87 $\pm$ 9.7	< 0.001
F.C.	0.50 $\pm$ 1.3	2.10 $\pm$ 4.1	< 0.001
B.E.	0.25 $\pm$ 1.3	0.33 $\pm$ 1.5	< 0.001
O-P	0.63 $\pm$ 2.0	0.04 $\pm$ 0.3	N.S.

Table 3.38 : Correlations of the percent areas of the various forms of cartilage change in the trochlea and patella. n = 67

Variable	p	r	Regression
INTACT	< 0.001	0.7136	29.2 + 0.80 Pat = Tro
SLIGHT	N.S.	0.2369	17.42 0.17 Pat = Tro
MODERATE	< 0.002	0.3825	6.62 + 0.39 Pat = Tro
SEVERE	< 0.001	0.5485	1.39 + 0.35 Pat = Tro
F.C.	< 0.03	0.2835	0.30 + 0.09 Pat = Tro
B.E.	< 0.001	0.5819	-0.01 + 0.8 Pat = Tro
O.P.	< 0.02	0.3001	0.60 + 0.90 Pat = Tro

F.C. - fibrocartilage, B.E. - bone exposure, O-P - osteophytes. N.S. - Not Significant, Pat - Patella , Tro - Trochlea

Table 3.39 : Comparison of the percent areas of the various forms of cartilage changes seen in the medial femoral condyle and the medial tibial plateau. Values given as mean $\pm$ standard deviation. Comparison made using a paired t-test.

Variable	Medial Femur	Medial Tibia	p
INTACT	59.62 $\pm$ 23.1	60.0 $\pm$ 20.2	N.S.
SLIGHT	19.51 $\pm$ 11.7	20.26 $\pm$ 11.1	N.S.
MODERATE	3.82 $\pm$ 12.3	14.54 $\pm$ 11.9	< 0.001
SEVERE	3.31 $\pm$ 5.6	1.36 $\pm$ 3.4	< 0.001
F.C.	0.55 $\pm$ 1.9	0.08 $\pm$ 0.4	< 0.04
B.E.	0.52 $\pm$ 3.3	0.17 $\pm$ 0.8	N.S.
O-P	2.77 $\pm$ 7.3	2.37 $\pm$ 5.1	< 0.004

Table 3.40 : Correlations of the percent areas of the various forms of cartilage change in the medial femoral condyle and medial tibial plateau. n = 67

Variable	p	r	Regression
INTACT	< 0.001	0.7919	0.54 + 0.95 MT = MF
SLIGHT	< 0.02	0.2922	13.16 + 0.31 MT = MF
MODERATE	< 0.001	0.5594	6.51 + 0.50 MT = MF
SEVERE	< 0.001	0.4632	2.09 + 0.90 MT = MF
F.C.	N.S.	0.1648	0.55 - 0.05 MT = MF
B.E.	< 0.001	0.7957	0.45 + 0.69 MT = MF
O-P	< 0.02	0.6332	1.14 + 0.68 MT = MF

F.C. - fibrocartilage, B.E. - bone exposure, O-P - osteophytes. N.S. - Not Significant, MF - Medial Femur, MT - Medial Tibia.

Table 3.41 : Comparison of the percent areas of the various forms of cartilage changes seen in the lateral femoral condyle and the lateral tibial plateau. Values given as mean ± standard deviation. Comparison made using a paired t-test.

Variable	Lateral Femur	Lateral Tibia	p
INTACT	63.39 ± 20.3	55.45 ± 20.9	< 0.001
SLIGHT	22.22 ± 14.0	17.44 ± 9.8	< 0.001
MODERATE	12.28 ± 13.2	19.05 ± 13.0	< 0.03
SEVERE	1.14 ± 6.5	4.25 ± 6.7	< 0.001
F.C.	0.26 ± 1.0	1.40 ± 2.3	< 0.001
B.E.	0.06 ± 0.5	0.15 ± 1.2	< 0.001
O-P	1.57 ± 4.5	2.37 ± 6.6	< 0.01

Table 3.42 : Correlations of the percent areas of the various forms of cartilage change in the lateral femoral condyle and lateral tibial plateau. n = 67

INTACT	< 0.001	0.7791	2.39 + 0.84 LF = LT
SLIGHT	< 0.02	0.2865	14.59 + 0.12 LF = LT
MODERATE	< 0.001	0.5316	1.95 + 0.54 LF = LT
SEVERE	< 0.03	0.2843	-1.45 + 0.60 LF = LT
F.C.	< 0.05	0.2495	1.18 + 0.41 LF = LT
B.E.	< 0.001	0.7125	-0.003 + 0.44 LF = LT
O-P	< 0.001	0.6125	0.24 + 0.50 LF = LT

F.C. - fibrocartilage, B.E. - bone exposure, O-P - osteophytes. LF - Lateral Femur, LT - Lateral Tibia.

Significant positive correlations for the percentage areas of all cartilage parameters were found between the lateral femoral condyle and lateral tibial plateau (Table 3.42).

Intra-femoral comparison

There were significant differences between the medial and lateral femoral condyles in the main study group for the percentage areas of slight, moderate and severe fibrillation and the percentage areas of osteophytes (Table 3.43).

Significant positive correlations were found between the two femoral condyles for percentage areas of intact cartilage, and all forms of cartilage damage except fibrocartilage (Table 3.44).

Intra-tibial comparison

In the main study group, the lateral tibial plateau has significantly greater percentage areas of slight and severe fibrillation, fibrocartilage, bone exposure and osteophytes than the medial tibial plateau on paired t-testing. The medial tibial plateau also has a significantly greater percentage area of intact cartilage than the lateral tibial plateau (Table 3.45).

Significant positive correlations existed between the two plateaux for the percentage areas of intact cartilage, slight and moderate fibrillation, bone exposure and osteophytes (Table 3.46).

Table 3.43 : Comparison of the percent areas of the various forms of cartilage changes seen in the medial and lateral femoral condyles. Values given as mean ± standard deviation. Comparison made using a paired t-test.

Variable	Medial Femur	Lateral Femur	p
INTACT	59.62 ± 23.1	63.39 ± 20.3	N.S.
SLIGHT	19.51 ± 11.7	22.22 ± 14.0	< 0.001
MODERATE	3.82 ± 12.3	12.28 ± 13.2	< 0.001
SEVERE	3.31 ± 5.6	1.14 ± 6.5	< 0.001
F.C.	0.55 ± 1.9	0.26 ± 1.0	N.S.
B.E.	0.52 ± 3.3	0.06 ± 0.5	N.S.
O-P	2.77 ± 7.3	1.57 ± 4.5	< 0.004

Table 3.44 : Correlations of the percent areas of the various forms of cartilage change in the medial and lateral femoral condyles. n = 67

Variable	p	r	Regression
INTACT	< 0.001	0.6527	7.88 + 0.82 LF = MF
SLIGHT	< 0.001	0.4286	11.67 + 0.35 LF = MF
MODERATE	< 0.001	0.4953	8.47 + 0.44 LF = MF
SEVERE	< 0.02	0.2950	3.35 - 0.03 LF = MF
F.C.	N.S.	0.1999	0.46 - 0.33 LF = MF
B.E.	< 0.001	0.4241	0.12 + 6.25 LF = MF
O-P	< 0.001	0.7747	1.19 + 1.01 LF = MF

F.C. - fibrocartilage, B.E. - bone exposure, O-P - osteophytes. N.S. - Not Significant, LF - Lateral Femur, MF - Medial Femur.

Table 3.45 : Comparison of the percent areas of the various forms of cartilage changes seen in the medial and lateral tibial plateaux. Values given as mean $\pm$ standard deviation. Comparison made using a paired t-test.

Variable	Medial Tibia	Lateral Tibia	p
INTACT	60.08 $\pm$ 20.2	55.45 $\pm$ 20.9	< 0.02
SLIGHT	20.26 $\pm$ 11.1	17.44 $\pm$ 9.8	< 0.001
MODERATE	14.54 $\pm$ 11.9	19.05 $\pm$ 13.3	N.S.
SEVERE	1.36 $\pm$ 3.4	4.25 $\pm$ 6.7	< 0.001
F.C.	0.08 $\pm$ 2.3	1.40 $\pm$ 2.3	< 0.001
B.E.	0.17 $\pm$ 0.8	0.15 $\pm$ 1.2	< 0.001
O-P	2.37 $\pm$ 5.1	2.37 $\pm$ 6.6	N.S.

Table 3.46 : Correlations of the percent areas of the various forms of cartilage change in the medial and lateral tibial plateaux. n = 67

Variable	p	r	Regression
INTACT	< 0.001	0.6509	20.48 + 0.71 LT = MT
SLIGHT	< 0.02	0.2911	14.98 + 0.33 LT = MT
MODERATE	< 0.001	0.5756	4.47 + 0.52 LT = MT
SEVERE	N.S.	0.0669	0.004 + 0.03 LT = MT
F.C.	N.S.	0.2057	1.25 + 0.02 LT = MT
B.E.	< 0.02	0.3141	0.17 - 0.01 LT = MT
O-P	< 0.001	0.5600	1.04 + 0.49 LT = MT

F.C. - fibrocartilage, B.E. - bone exposure, O-P - osteophytes. N.S. - Not significant, MT - Medial Tibia, LT - Lateral Tibia.

3.3 The Menisci

In all cases examined the menisci were present and there were no tears or other obvious injury.

The position and extent of the menisci was mapped in 24 of the knees obtained from females, and 39 of those obtained from males. The mean percentage area of tibial plateau covered was significantly greater in the lateral tibial plateau (mean value 82.95 ± 6.0 mm^2) than in the medial tibial plateau (mean value 67.63 ± 8.2 mm^2, $p < 0.0001$). No significant differences were seen in the percentage areas covered between right and left, or between males and females. There was no correlation between age and the percentage area covered, or between percentage area of intact cartilage and the percentage area covered by menisci in either medial or lateral tibial plateaux.

3.4 DISCUSSION

One of the most striking findings of this study was the higher frequency and the greater extent of degenerative changes in the knees of females compared to those of males. These differences were most marked in the medial femoral condyle, and least in the patella where the only difference between the sexes was in the articular surface area (Table 3.13). Neither Keefer et al [61] or Keyes [63] in their work on age-related changes in the knee remarked on any sex-related differences. Meachim et al [88] did find a greater frequency of cartilage damage in the patellofemoral joint in females, but in the present study a greater frequency of damage has also been described in the medial compartment of the tibiofemoral joint. This difference parallels the sex-related difference in the frequency of osteoarthritis of the knee and could be the result of the smaller articular surfaces in the knees of women, so that loading forces passing through the joint are concentrated over smaller areas, with a greater force per unit area and thus with an increased likelihood of cartilage damage. It could be argued that this concentration would be compensated for by the smaller forces acting in women as a result of their generally smaller body weights, but Nissel et al [98] have determined that, for individuals of the same weight, larger forces develop in the knees of females than in males, due to the shorter patellar moment arm. This, combined with the smaller areas over which such forces would be exerted, may explain the higher frequency of age-related cartilage changes in females.

The presence of widespread correlations between the percentage areas of moderate fibrillation, severe fibrillation, fibrocartilage, bone exposure and osteophytes, was in marked contrast to the paucity of significant correlations of any of these cartilage parameters with slight fibrillation. While this may be the result of inconsistencies in the assessment of slight fibrillation, it seems unlikely. Alternatively, this finding may indicate a significant difference in the nature of slight fibrillation compared to other forms of cartilage damage. Slight fibrillation

may represent the non-progressive cartilage lesion described by Byers et al [16] in that it is predominantly found in the peripheries of articular surfaces, whilst the other categories of degeneration may represent the various stages in the development of the progressive changes associated with weight-bearing [16], which are more typically seen in the loaded areas of a joint. The difference between these various forms of cartilage change is highlighted by the fact that while the percent area of slight fibrillation increases linearly with age, the other forms of cartilage change show a non-linear relationship with age, such that the nett increase in the percent area of progressive changes is greater in the elderly than in the young. Thus, although cartilage degeneration occurs throughout life, a point is reached where protective factors or attempts at repair become less effective and age-related cartilage change develops at an accelerated rate. This is most marked in the patella, where the percentage areas of advanced cartilage changes such as moderate and severe fibrillation and fibrocartilage develop rapidly after the age of 65-70 years (Figures 3.26,3.31, 3.36). Of note, the deterioration in cartilage condition begins early in adult life; as can be seen from Figures 3.2 to 3.13 an entirely intact articular surface is not a normal state affairs from early adult life onwards, and overt cartilage changes can be seen from the third and fourth decades onwards.

The study of age-related degeneration within the femoral condyles has been less exhaustive than the study of changes elsewhere in the knee. The main facts determined by previous workers are the higher frequency of overt changes on the medial, as opposed to the lateral, condyle [7,61,63]; the presence of a focal lesion along the inner aspect of the medial condyle [7,61]; and the relative sparing of the posterior aspects of the condyles [63]. The current study confirms that changes such as severe fibrillation, fibrocartilage formation and bone exposure are more frequent on the medial condyle, but there are no significant differences in the percentage areas affected between the medial and lateral condyles.

Differences in the zones affected by advanced cartilage changes also exist. Severe fibrillation is far more common within the lateral zone of the medial condyle than anywhere else within the femur, whilst bone exposure is seen most frequently in the anterior zones of the medial femur, but only in the central zone of the lateral condyle (Table 3.3 and 3.4). Keefer et al [61] considered that the lesion in the lateral zone of the medial condyle lesion was the result of articulation with the intercondyloid eminence of the tibia, but Goodfellow et al [47] determined that this area articulates with the patella during flexion. The patella also articulates with the lateral condyle, but full thickness cartilage loss is not seen. This can be explained by the fact that the convex medial facet of the patella will articulate with the convex surface of the medial condyle, and this will exert large stresses on the hyaline cartilage. In contrast, the lateral facet of the patella is typically concave, and thus its articulation with the convex lateral condyle will be more congruous and less damaging to the cartilage [148]. The anterior zone of the medial condyle has been determined to be the area of contact when the tibiofemoral joint is in a neutral position and therefore, it will be the point of contact during the moment of heel strike in walking and will be exposed to forces of up to 3 times body weight [95]. The central areas in both lateral and medial condyles are affected by fibrocartilage and bone exposure with equal frequency and represent the areas that are loaded when the knee is between 30 and 60 degrees of flexion [144]; a range of movement that is frequently used in daily life during, for example, walking and climbing up and down stairs [95]. Thus the zones of high loading within the femoral condyles are also the areas of advanced cartilage change, as described by Byers et al in the hip [16]. The medial zone of the medial femoral condyle is not an area of high loading and yet full thickness loss was seen here in two specimens. In both cases, the area affected was adjacent to florid osteophyte growth. Progressive changes, therefore, appear to occur in this region only in the presence of a distortion of the normal joint anatomy when the mechanics and loading of the condyle may be substantially altered.

Previous studies on the pattern of degeneration in the tibial plateaux [7,61,63] have described a higher frequency of overt damage on the lateral, as opposed to the medial, plateau, and the current study has confirmed that severe fibrillation and fibrocartilage formation are far more frequent in the lateral tibia (Tables 3.5 and 3.6). The presence of a greater percentage area of overt damage on the medial plateau, described by Meachim [83], was not confirmed by this study which found that the percentage areas of severe fibrillation and bone exposure were not significantly different (Tables 3.24 and 3.30) and that the area of fibrocartilage formation was significantly greater on the lateral plateau of the tibia (Table 3.27); in fact in no case was fibrocartilage formation seen in the medial tibial plateau. This is entirely the result of the high frequency of discrete areas of damage beneath the posterior horn of the lateral meniscus, as described by Meachim [83] and Bullough and Walker [15]. In 23 of the 87 lateral tibial plateau examined in this study there was a discrete oval lesion of fibrocartilage formation in this position, and in 3 cases there was full thickness loss. In contrast, in the medial plateau progressive changes were limited to the uncovered area; bone exposure was seen only in the uncovered regions in only two cases. This lesion beneath the posterior horn of the lateral meniscus would appear to disprove the long held concept of menisci protecting against the development of cartilage damage [60,62,66,125,143]. In the other meniscal covered regions of both tibial plateaux, however, the menisci do appear to protect underlying cartilage, while the uncovered area shows the earliest and most severe cartilage change. It is unclear why the posterior zone of the lateral plateau is vulnerable to damage : this area is loaded when the knee is flexed to approximately 120 degrees [144] and will thus be exposed to potentially damaging forces when people arise from a chair. At the same time, however, the medial plateau will also be subjected to a greater load since the medial compartment of the knee carries more of the load even in the presence of knee joint deformity [62], and whilst the area of contact in the medial plateau is over the uncovered area [144] no discrete advanced cartilage lesions are seen there. This may be because the contact area

between the tibia and femur is greater on the medial side and the forces, although of a greater magnitude, acting over a larger area are less damaging [51]. Alternatively, if the compliance of cancellous bone is an important factor in the absorption of forces potentially damaging to the cartilage [112], then the relative lack of cancellous bone beneath the posterior aspect of the lateral tibia, and the distortion due to the underlying tibiofibular joint, may render the cartilage of the posterior zone of the lateral tibia vulnerable to damage. A number of workers have in fact found that the strength and stiffness of bone is significantly greater in the posterior aspect of the lateral plateau, compared to elsewhere in the tibia [44,57,58], and it can be proposed that this is a result of distortion of the small volume of cancellous bone present in this area.

The tibial plateaux differed from the other regions of the knee in that cartilage changes were restricted to certain areas, typically the uncovered zones and, in the case of the lateral plateau, the posterior zone. In contrast, cartilage changes were more widespread in the femoral condyles. Examination of the tibiofemoral joint reveals that the contact areas on the femur range over a larger area than they do in the tibia [144], which may explain the relative localisation of cartilage changes in the tibia. This localisation allows speculation on the development of age-related cartilage changes which would appear to commence with the formation of fissures, followed by the development of severe fibrillation and eventual bone exposure and fibrocartilage formation (Figure 3.9).

Comparison of the frequency of overt cartilage changes within the two compartments of the tibiofemoral joint reveals that whilst severe fibrillation, fibrocartilage formation and bone exposure are more frequent in the medial femoral condyle than the medial tibial plateau (Tables 3.4 and 3.6), the opposite is true in the lateral compartment where overt change is more common within the tibia (Tables 3.5 and 3.7). Whilst the difference in the lateral compartment can be explained in terms of the fact that contact areas within the tibia are far more restricted in the tibia than the femoral condyle, so that loading forces are more

concentrated, this cannot explain the findings within the medial compartment, which are due to the frequent advanced changes within the lateral zone as the result of articulation with the patella, and the changes in the anterior zone due to the loading during the heel strike phase of walking. These results highlight the fact that because two articular surfaces are in contact and exposed to similar loading forces, the distribution and severity of age-related cartilage changes cannot be assumed to be identical.

The present study found that the development of degeneration within the trochlea follows a pattern similar to that described by Meachim and Emery [88]. Initial changes around the periphery, are followed by involvement of the central and notch zones [7,61] and there is a sparing of the lateral aspect of the trochlea until late in life [88] (Figures 3.10 and 3.11). Progressive changes were found to predominate in areas of high loading: severe fibrillation and bone exposure are seen most commonly in the central zone, whilst fibrocartilage formation is seen with equal frequency in the medial, lateral and central zones (Table 3.7). This is in contrast to previous work which found full thickness cartilage loss restricted to the central and lateral zones. There was no correlation between the percentage area of osteophytes and bone exposure as described by Emery and Meachim [32].

The current study found the patella to have the highest frequency of all forms of cartilage change in the knee and to have significantly greater percentage areas of slight and moderate fibrillation and fibrocartilage formation (Tables 3.18, 3.21 and 3.27). The localisation of non-progressive changes to the periphery of the patella seen in Figures 3.12 and 3.13 have been described previously [2]. Bone exposure was found only in the central and medial aspects of the patella, in contrast to previous workers who found that full-thickness cartilage loss to be characteristic of the lateral facet [2,32,84,88]. Meachim [88] noted that severe cartilage changes found in early life were typically present on the medial facet of the patella, whereas, in the present work, such changes were most frequently found on the central ridge of the patella in the under 50 age group. This difference between the frequency of

cartilage changes in the medial and central zones of the patella found here compared to elsewhere [88], may be the result of differences in the manner in which the patella was divided in the two studies, but the difference between the medial and lateral facets cannot be readily explained. The presence of full thickness cartilage loss with bone exposure is an unambiguous feature, not open to interpretation or affected by variations in India ink technique. The populations studied do not appear to be different: although the current work did include 4 specimens obtained from Aboriginal Australians the population was 94% Caucasian and the male to female ratio was very similar to the Meachim study [88]. The result could reflect differences in the functional demands on the knees between these two study groups, but this seems unlikely. The high frequency of damage on the medial facet is to be expected, as the medial facet of the patella articulates with the medial femoral condyle when the knee is flexed beyond 90 degrees and, as described earlier, the articulation of two convex surfaces promotes cartilage damage [148].

As in the case of the tibiofemoral joint, although they articulate with one another the trochlea and patella differ significantly in the frequency and extent of age-related cartilage change : the patella is more frequently affected by severe fibrillation, fibrocartilage formation and bone exposure than the trochlea, and displays significantly greater percentage areas of moderate and severe fibrillation and fibrocartilage formation. These differences may be due to the smaller area of the patella, so that the loading forces will be concentrated onto a smaller area of the articular surface than it does in the trochlea. The higher frequency of advanced forms of damage in the patella may also relate to the fact that, while the patella articulates with both the trochlea and the femoral condyles during the normal range of movement of the knee, the trochlea is not always in contact with the patella and is not always exposed to loading and potentially destructive forces.

The patellofemoral joint is the area of the earliest and most rapid age-related degeneration within the knee. Figures 3.16-3.18 show that the nett loss of

percentage intact cartilage is far greater in the patella and trochlea than elsewhere, and the extent and frequency of more advanced cartilage changes such as moderate and severe fibrillation and fibrocartilage formation is generally higher. This high frequency occurs despite the fact that the forces acting across the patellofemoral joint are less than those experienced across the tibiofemoral joint [100]. The concentration of loading forces is of course much greater in the patellofemoral joint, since the weight bearing forces across the tibio-femoral joint are transmitted across both lateral and medial compartments, which are also partly protected from loading forces by the menisci [100]. Once degeneration begins in the patellofemoral joint, the process is undoubtedly accelerated by the high shear forces existing in this joint in comparison to the tibiofemoral joint, and the excursion of the patella across the trochlea.

It can be seen from the results presented here that cartilage condition deteriorates from early adult life onwards; that this deterioration occurs to a significantly greater extent in females as opposed to males and to a greater extent in the patellofemoral joint than in the tibiofemoral joint. The question that now needs to be addressed is whether these regional, sex- and age-related differences in cartilage condition are reflected by differences in the structure of the bone-cartilage interface, subchondral vascularity or the structure of subchondral bone.

CONCLUSIONS

1. Cartilage condition within all compartments of the knee deteriorates with increasing age, and this change begins in early adult life.

2. Cartilage damage is more frequent and more extensive in females than in males, and this difference is most marked in the medial femur and least marked in the patella and medial tibia.

3. The frequency of moderate and severe fibrillation, fibrocartilage formation, bone exposure and osteophytes, increases markedly with age, whereas the rate of development of slight fibrillation is the same throughout life. Slight fibrillation represents the non-progressive cartilage damage of Byers et al [16], which is typically seen in areas of low loading, compared to the other categories of cartilage damage which represent progressive changes in areas of increased loading.

3. The distribution of progressive changes such as severe fibrillation, fibrocartilage formation and bone exposure appear restricted to areas of high loading within all regions of the knee.

4. The patella has the highest frequency of all forms of age-related change, and the greatest percentage areas of slight, moderate and severe fibrillation and fibrocartilage formation.

5. The medial femoral condyle is more frequently affected by age-related cartilage change than the lateral condyle and this difference is due to the high frequency of advanced cartilage changes in the lateral zone as the result of the articulation of the patella.

6. Degenerative changes within the lateral tibial plateau are more severe than those in the medial plateau due to the failure of the meniscus in the posterior aspect of the plateau to fully protect the underlying cartilage. This localisation of cartilage damage may be related to the distortion of the underlying cancellous bone by the tibiofibular joint.

-7. Significant differences in the pattern and severity of cartilage damage between articulating surfaces are seen in both the patellofemoral and tibiofemoral joints, thus it cannot be assumed that articulating surfaces will respond identically to the same loading forces.

8. The patellofemoral joint has a greater frequency of cartilage damage than the tibiofemoral joint despite the smaller forces acting across it. This may be due to the shearing nature of the forces acting across the patellofemoral joint, to the smaller areas over which loading forces act or to other yet undefined factors.

CHAPTER FOUR : QUANTITATION OF THE BONE-CARTILAGE INTERFACE

There are a number of hypotheses concerning the initiation of cartilage damage : it has been proposed that the loss of proteoglycans from the matrix can result in cartilage degeneration [37] , that decreases in the number of subchondral vessels can affect the nutrition of the deeper layers of cartilage causing cartilage to become damaged [28,29,54,59], or that increases in bone density render the overlying cartilage sensitive to loading forces [111,112]. In this study these factors have been examined histologically and quantitated to clarify the origin of age-related cartilage changes.

RESULTS

A total of 132 blocks were examined, from the medial femoral condyle, medial tibial plateau, trochlea and patella of the 33 individuals in Group 1. The parameters examined were the total cartilage thickness, the Mankin score, the thickness of the calcified cartilage, the density of the subchondral plate, the irregularity of the tidemark and the osteochondral junction, as well as the number of tidemarks and the number of focal contacts (Table 4.1). There were no significant differences between the male and female groups for any of these parameters (Table 4.2). There were no significant differences between specimens from the right and left knees except for total cartilage thickness which was significantly greater on the right (Table 4.3).

4.1 Mankin Score

The Mankin score showed no significant variation between the four regions examined (Table 4.4), but showed a significant positive correlation with age (Figure 4.1). This correlation was significant in all four regions of the knee examined, except for the medial femur (Figure 4.2).

Table 4.1 : Table of the mean values of the various parameters examined in the decalcified blocks in the main study group. Values expressed as mean ± standard deviation.
OCJ - Osteochondral junction

PARAMETER	MEAN ± S.D.
MANKIN SCORE	6.34 ± 2.5
TIDEMARKS	2.52 ± 1.4
FOCAL CONTACTS	9.23 ± 3.9
TOTAL CARTILAGE THICKNESS (microns)	2579.03 ± 1076.6
SUBCHONDRAL PLATE THICKNESS (microns)	600.48 ± 135.9
CALCIFIED CARTILAGE THICKNESS (microns)	146.95 ± 52.3
OCJ IRREGULARITY	2.70 ± 0.6
TIDEMARK IRREGULARITY	15.2 ± 0.1

Table 4.2 : Comparison of the parameters from the decalcified blocks in males and females.

	Males n = 80	Females n = 52	p
MANKIN SCORE	6.35 ± 2.6	6.33 ± 2.4	NS
TIDEMARK	2.66 ± 1.5	2.38 ± 1.4	NS
FOCAL CONTACTS	9.74 ± 4.0	8.46 ± 3.6	NS
TOTAL CART.	2697.95 ± 1156.2	2396.07 ± 921.3	NS
S.C.P	604.00 ± 129.0	595.07 ± 146.9	NS
CALC. CART	138.90 ± 44.7	159.33 ± 60.5	NS
OCJ/TL	2.64 ± 0.5	2.79 ± 0.7	NS
TM/TL	1.52 ± 0.1	1.53 ± 0.1	NS

SCP - Subchondral plate thickness
Calc Cart - Calcified cartilage thickness
OCJ/TL - Osteochondral junction irregularity
TM/TL - Tidemark irregularity

Table 4.3 : Comparison of parameters taken from the right and left knees,

	Left n = 68	Right n = 64	p
MANKIN SCORE	6.27 ± 2.4	6.48 ± 2.5	NS
TIDEMARK	2.45 ± 1.4	2.65 ± 1.5	NS
FOCAL CONTACTS	9.76 ± 3.9	8.31 ± 3.7	NS
TOTAL CART.	2719.59 ± 1142.3	2333.08 ± 910.5	< 0.03
S.C.P	601.77 ± 128.6	598.23 ± 149.1	NS
CALC. CART	136.14 ± 45.4	165.87 ± 58.4	NS
OCJ/TL	2.62 ± 0.5	2.85 ± 0.7	NS
TM/TL	1.51 ± 0.1	1.54 ± 0.1	NS

Table 4.4 : Mankin Scores from the four regions of the knee examined.

	MIN	25%ile	MEDIAN	75%ile	MAX
MF	0	5	6	8	10
MT	3	6	6	7	10
TR	2	3	4	9	11
PA	2	6	8	9	10

Multiple Wilcoxon rank tests : No significant regional differences.

Figure 4.1 : Graph of age versus Mankin Score in the main study group.

$n = 132$, $r = 0.4843$, $p < 0.0001$

Mankin Score = 2.95 = 0.06 Age

Figure 4.2 : Graph of age versos Mankin score in the four regions of the knee examined.

Medial Femur : $n = 33$, $r = 0.2967$, Not significant

Mankin Score = 3.44 + 0.05 Age

Medial Tibia : $n = 33$, $r = 0.5042$, $p < 0.01$

□ —·— Mankin Score = 3.44 + 0.05 Age

Trochlea : $n = 33$, $r = 0.4746$, $p < 0.01$

○ — — Mankin Score = 0.92 + 0.08 Age

Patella : $n = 33$, $r = 0.4367$, $p < 0.02$

✳ -- - -- Mankin Score = 4.00 + 0.05 Age
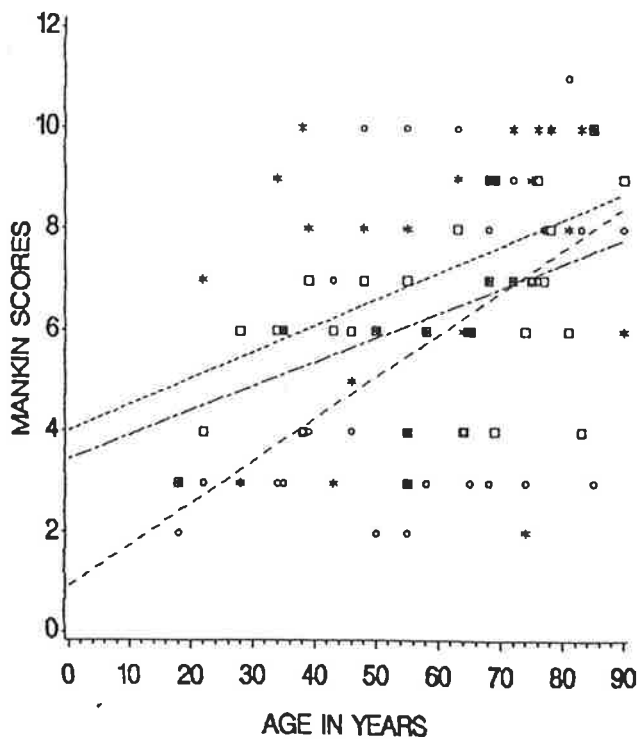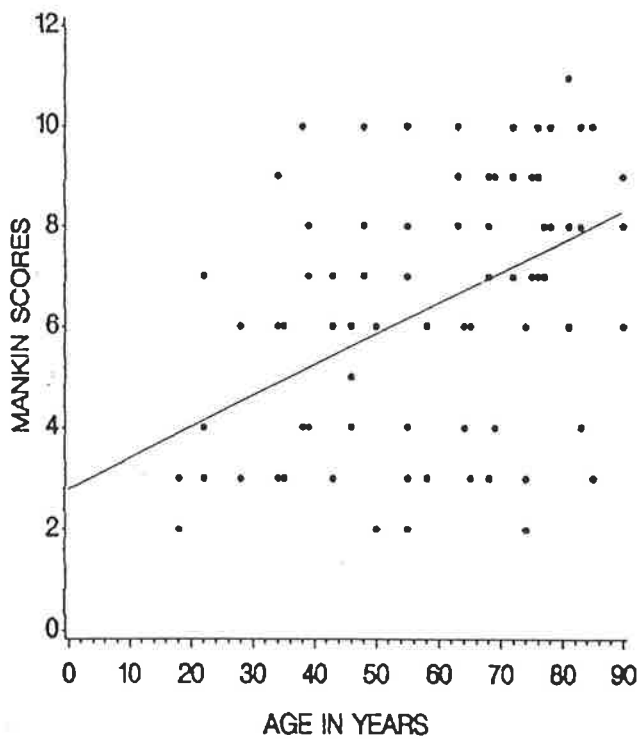
There was a significant negative correlation between Mankin scores and cartilage thickness (Figure 4.3). This correlation was significant only in the medial femur and trochlea (Figure 4.4).

4.2 Number of Tidemarks

The number of tidemarks was significantly lower in the medial tibia than elsewhere (Table 4.5).

There was a significant positive correlation between age and the number of tidemarks ($r = 0.3530$, $p < 0.0001$, $n = 132$), but this was significant regionally only in the patella ($r = 0.3801$, $p < 0.05$, $n = 33$).

A significant negative correlation was seen between the number of tidemarks and the thickness of the subchondral plate (Figure 4.5). This correlation was significant in the medial tibia but in none of the other regions ($r = -0.4485$, $p < 0.01$, $n = 33$).

4.3 Number of Focal Contacts

There were a significantly greater number of focal contacts in the trochlea than in the medial femur or medial tibia (Table 4.6).

There was no significant correlation between focal contact numbers and age. There was found to be a significant positive correlation between focal contact numbers and the irregularity of the osteochondral junction in the total study group (Figure 4.6), and regionally this was significant only in the medial femur ($r = -0.4350$, $p < 0.02$, $n = 33$). A significant positive correlation found between focal contact numbers and the irregularity of the tidemark in the total study group (Figure 4.7) was not significant in any region alone.

Figure 4.3 : Graph of Mankin Score versus total cartilage thickness in the main study group.

$n = 132, r = -0.3359, p < 0.0001$

Cartilage Thickness = 3499.80 - 145.2 Mankin Score

Figure 4.4 : Graph of Mankin Score versus total cartilage thickness in the four regions examined.

● ⸺ Medial Femur : $n = 33, r = -0.4286, p < 0.02$

Cartilage Thickness = 2978.96 - 140.3 Mankin Score

Medial Tibia : $n = 33, r = -0.2425$, Not significant

Cartilage Thickness = 3182.92 - 120.2 Mankin Score

○ ⸺ ⸺ ⸺ Trochlea : $n = 33, r = -3564, p < 0.02$

Cartilage Thickness = 3909.18 - 163.3 Mankin Score

Patella : $n = 33, r = -0.3359$, Not significant

Cartilage Thickness = 4055.47 - 174.8 Mankin Score
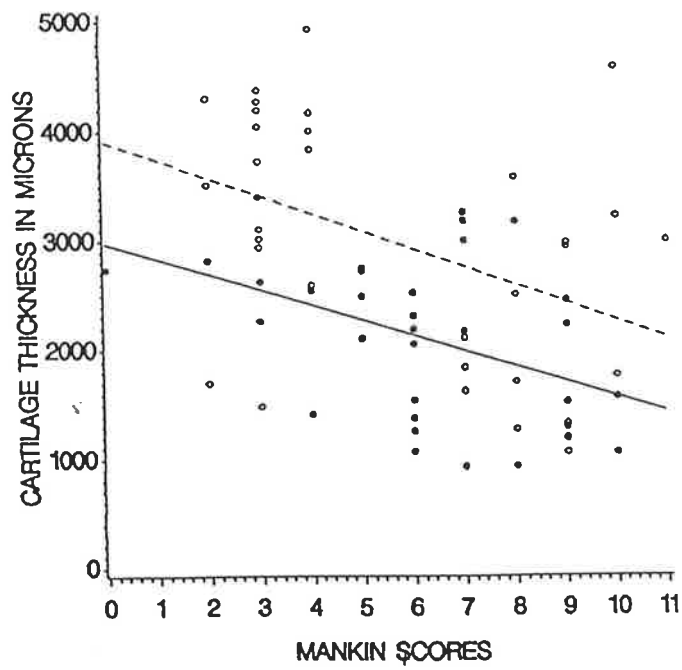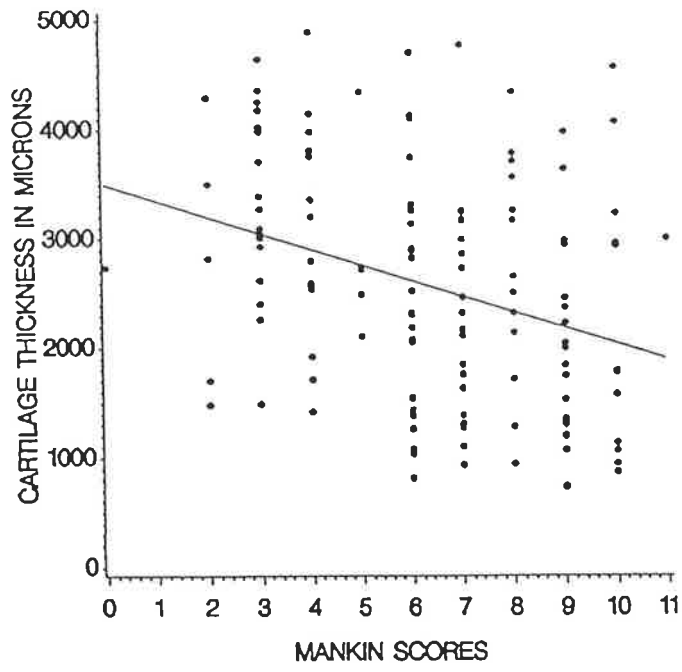
Table 4.5 : Tidemarks

	MIN	25%ile	MEDIAN	75%ile	MAX
MF	1	2	3	4	7
MT	1	1	1	2	4
TR	1	2	3	4	6
PA	1	2	2	3	6

Multiple Wilcoxon tests reveal significantly fewer tidemarks in the medial tibia than elsewhere (p < 0.001 in all cases)

Figure 4.5 : Graph of the number of tidemarks versus subchondral plate thickness in microns.

$n = 132, r = -0.2351, p < 0.01$

Subchondral plate thickness $= 686.25 - 34,0$ Tidemarks
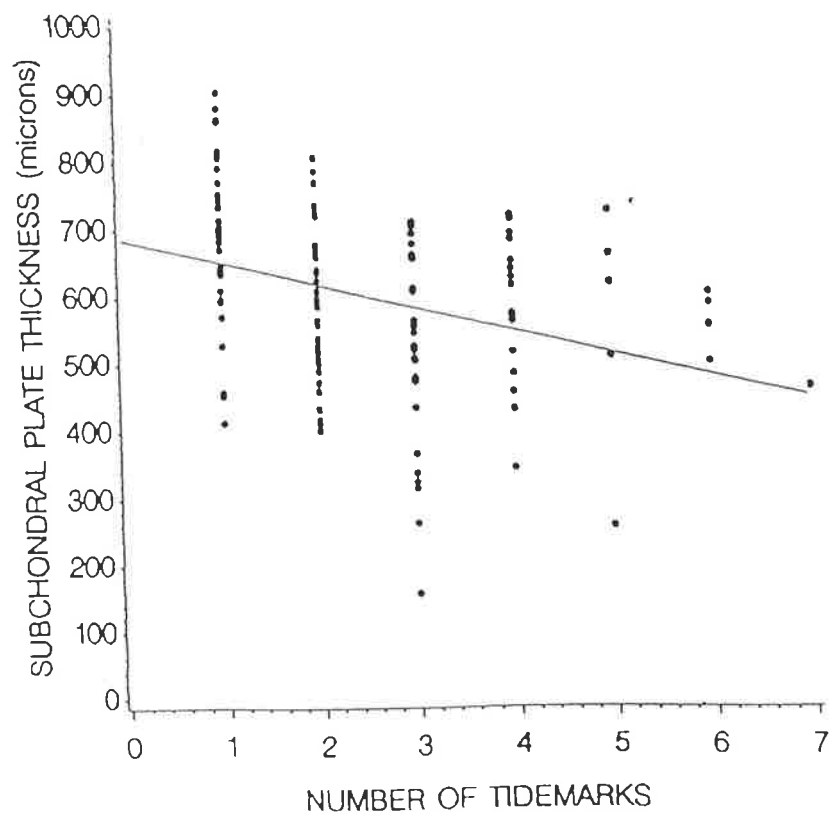
Table 4.6 : Focal Contacts

	MIN	25%ile	MEDIAN	75%ile	MAX
MF	1	5	8	11	17
MT	3	6	8	11	20
TR	5	8	11	12	18
PA	1	7	9	13	17

Multiple Wilcoxon rank tests : The number of focal contacts was significantly greater in the trochlea than either the medial femur or tibia ($p < 0.02$ in both cases).

Figure 4.6 : Graph of focal contact numbers versus the irregularity of the osteochondral junction.

$n = 132$, $r = 0.2419$, $p < 0.01$

OCJ Irregularity $= 2.37 + 0.04$ Focal Contacts
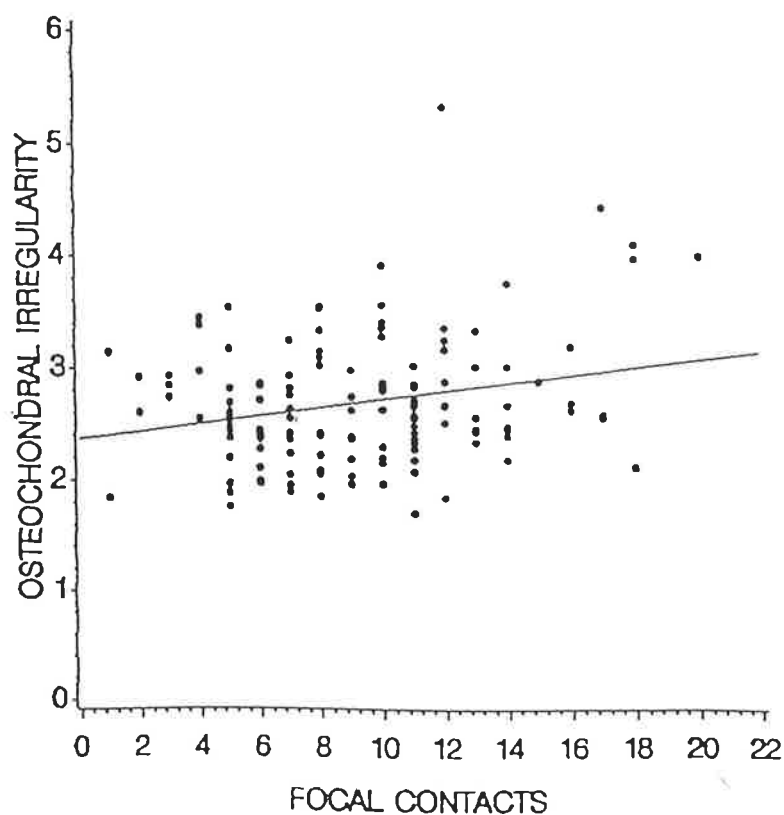
Figure 4.7 : Graph of the number of focal contacts versus the irregularity of the tidemark.

$n = 132, r = 0.1731, p < 0.05$

Tidemark irregularity = 1.47 + 0.005 Focal contacts
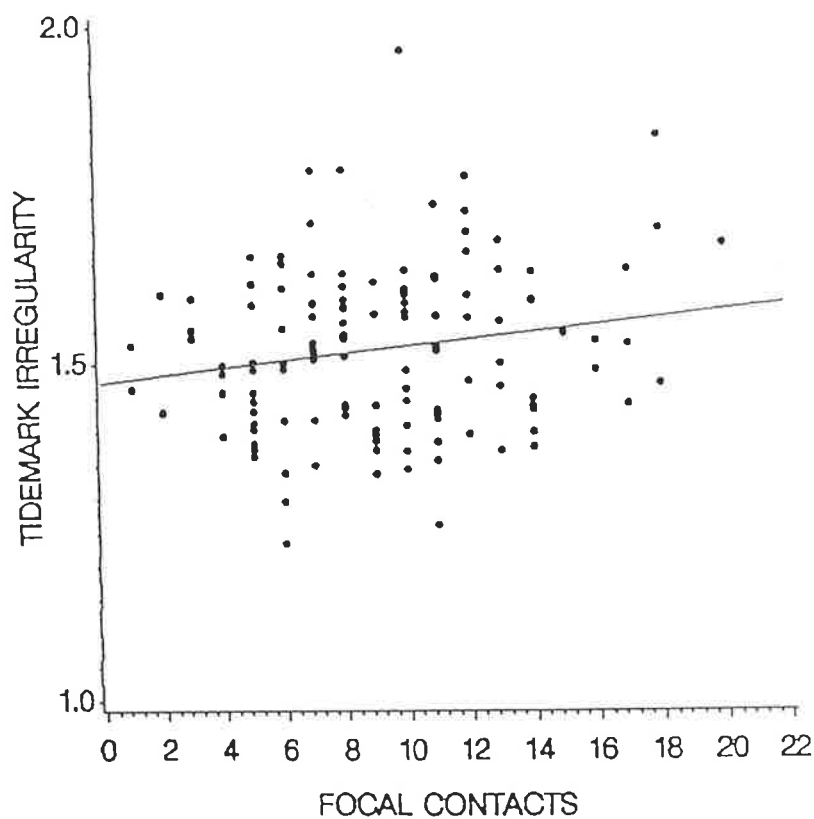
Table 4.7 : Cartilage Thickness

	MIN	25%ile	MEDIAN	75%ile	MAX
MF	934.43	1385.51	2233.96	2729.48	3407.21
MT	742.69	1756.59	2585.52	3033.80	4362.69
TR	1068.36	1771.25	3003.71	4011.03	4931.88
PA	727.55	1743.56	2933.96	3805.97	4820.41

Multiple Wilcoxon tests : Cartilage thickness was significantly greater in the patella and trochlea than in the medial femur ($p < 0.02$ in both cases).

4.4 Total Cartilage Thickness

The total thickness of cartilage was significantly greater in the patella and trochlea than in the medial femur or medial tibia (Table 4.7). A significant negative correlation was found between age and total cartilage thickness (Figure 4.8). This correlation was significant in all regions examined except the medial femur (Figure 4.9).

A significant positive correlation was found between total cartilage thickness and subchondral plate thickness (Figure 4.10). This correlation was not significant in any region alone.

Total cartilage thickness exhibited a significant positive correlation with the irregularity of the tidemark (Figure 4.11). The correlation was not significant in any region independently.

No significant correlations were seen between cartilage thickness and either the irregularity of the osteochondral junction, the number of tidemarks or the number of focal contacts.

4.5 Subchondral plate thickness

The thickness of the subchondral plate was significantly different in all regions examined; being greatest in the medial tibia, then the patella and the trochlea, and least in the medial femur (Table 4.8).

There was a significant negative correlation between age and subchondral plate thickness in the total study group (Figure 4.12) which was significant in all regions except the trochlea (Figure 4.13).

Subchondral plate thickness showed a significant positive correlation with the irregularity of the osteochondral junction in the total study group (Figure 4.14), but regionally this was significant only in the medial femur ($r = 0.4016$, $p < 0.05$, $n = 33$).

Figure 4.8 : Graph of age versus the total cartilage thickness in the main study group.

n = 132, r = - 0.4212, p < 0.0001

Cartilage Thickness = 3967.17 - 23.46 Age

Figure 4.9 : Graph of age versus total cartilage thickness in the four regions of the knee examined.

Medial Femur : n = 33, r = -0.3118, Not significant

Cartilage Thickness = 2853.33 - 12.4 Age

□ — · —   Medial Tibia : n = 33, r = - 0.4485, p < 0.02

Cartilage Thickness = 3611.47 - 20.0 Age

O — — —   Trochlea : n = 33, r = -0.3498, p < 0.05

Cartilage Thickness = 4288.98 - 22.6 Age

✳ - - - - -   Patella : n = 33, r = -0.5933, p < 0.001

Cartilage Thickness = 5114.95 - 38.8 Age
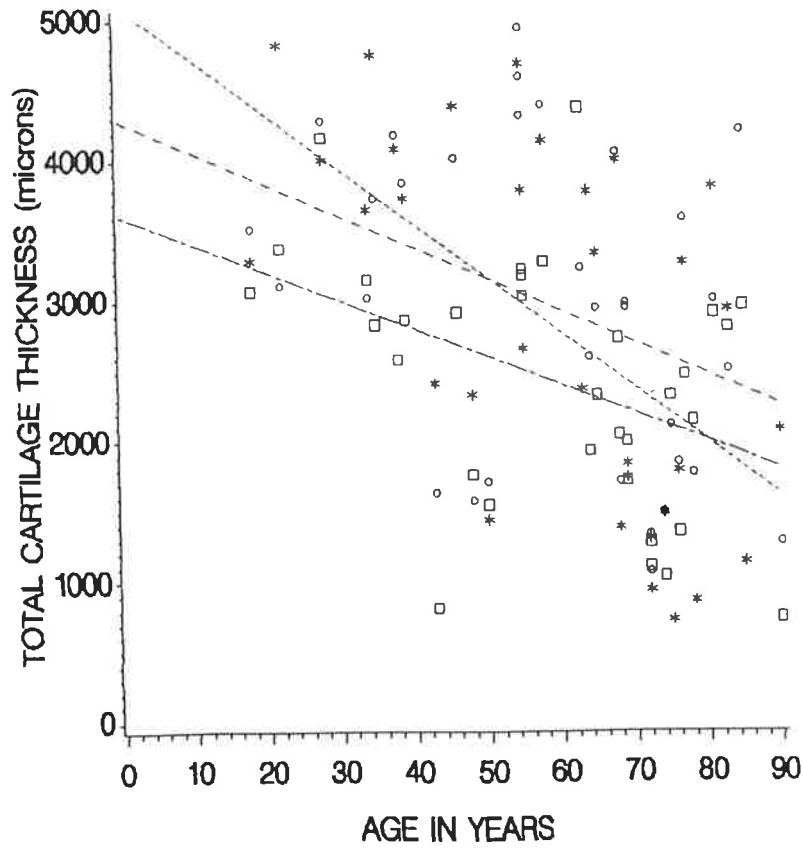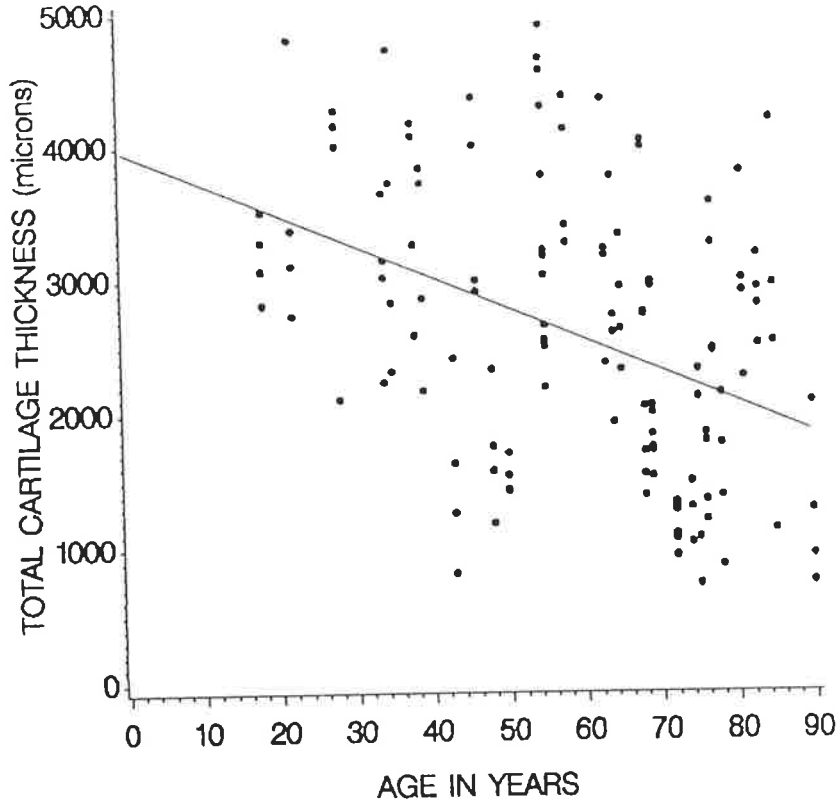
Figure 4.10 : Graph of total cartilage thickness versus subchondral plate thickness in the main study group.

$$n = 132, r = 0.2915, p < 0.02$$

SCP Thickness $= 523.11 + 0.03$ Cartilage Thickness

Figure 4.11 : Graph of total cartilage thickness versus tidemark irregularity in the main study group.

$$n = 132, r = 0.3564, p < 0.0001$$

Tidemark irregularity $= 1.42 + (3.9 \times 10^{-5})$ Cartilage
Thickness
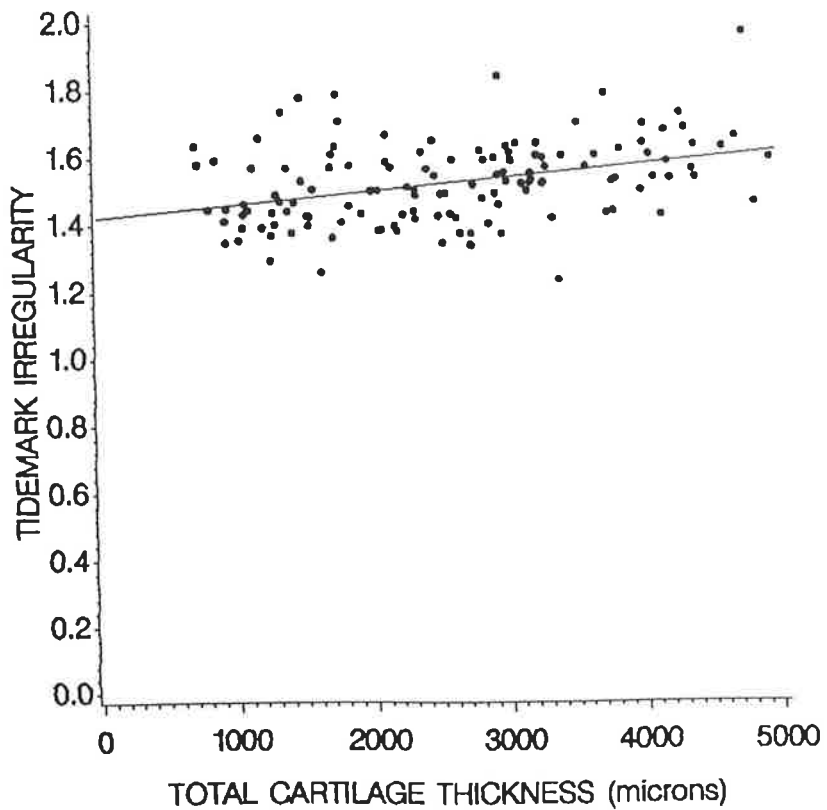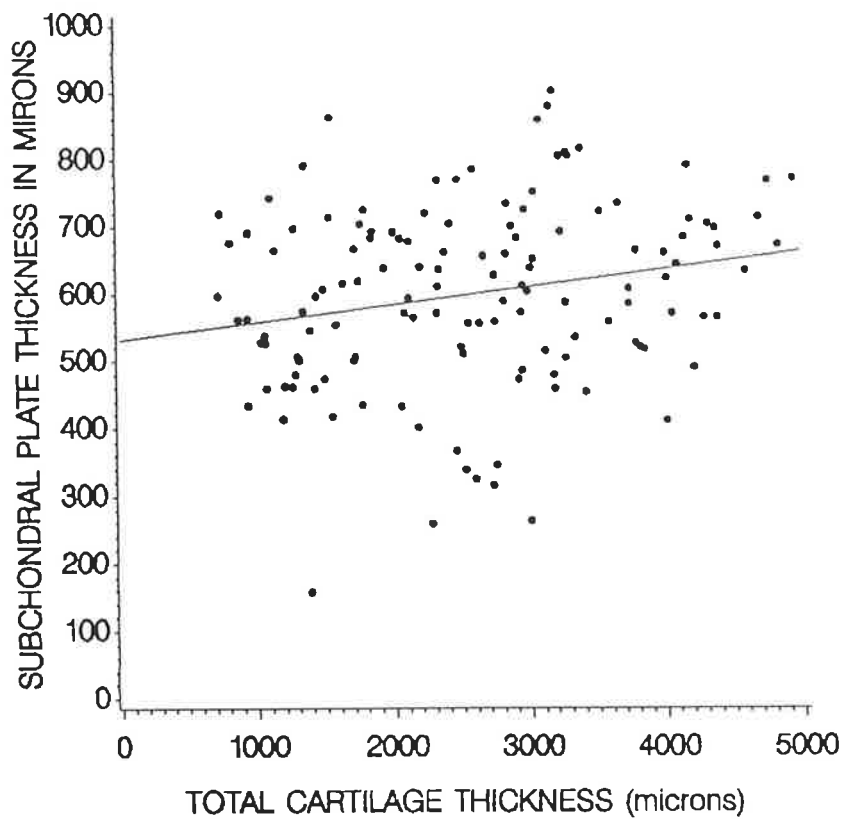
Table 4.8 Subchondral Plate Thickness

	MIN	25%ile	MEDIAN	75%ile	MAX
MF	157.66	413.44	461.08	556.7	719.95
MT	472.33	676.61	720.1	791.58	903.9
TR	352.22	510.69	574.62	667.3	771.29
PA	501.11	572.93	636.60	683.45	806.69

Multiple Wilcoxon rank tests :
    The subchondral plate is thinner in the medial femur than in any other region ($p < 0.009$)
    The subchondral plate is thicker in the medial tibia than elsewhere ($p < 0.001$)
    The subchondral plate is thicker in the patella than in the trochlea ($p < 0.05$).

Figure 4.12 : Graph of age versus subchondral plate thickness in the main study group.

    $n = 132, r = -0.2982, p < 0.001$

    SCP Thickness $= 727.56 - 2.15$ Age
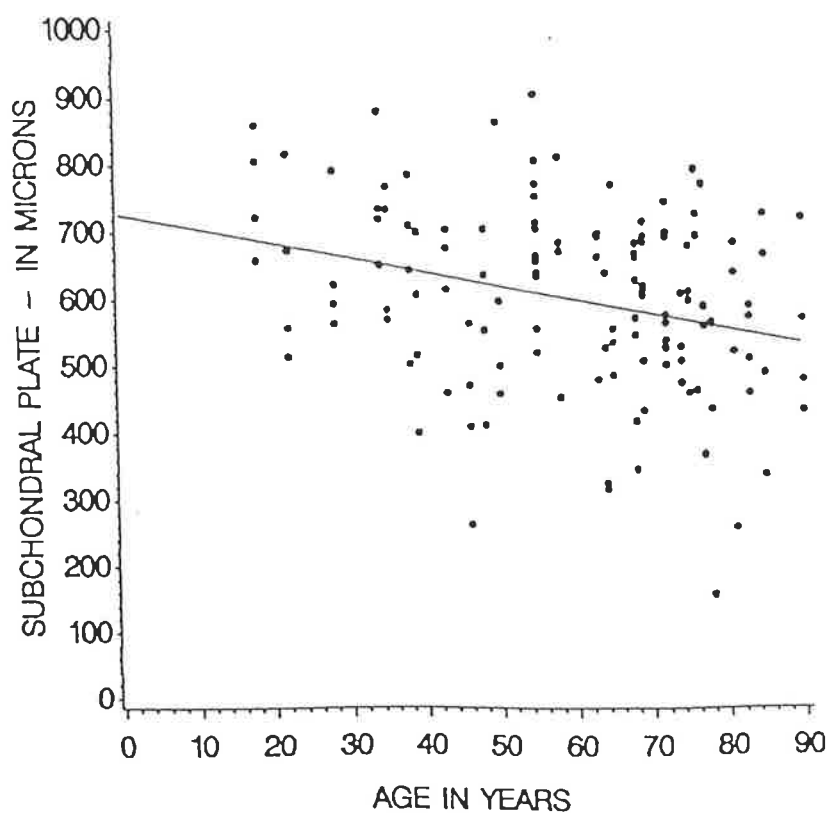
Figure 4.13 : Graph of age versus subchondral plate thickness in the four regions of the knee examined.

● ——
Medial Femur : n = 33, r = - 0.4640, p < 0.01

SCP Thickness = 651.38 - 3.0 Age

□ — · —
Medial Tibia : n = 33, r = -0.4550, p < 0.02

SCP Thickness = 859.51 - 2.4 Age

Trochlea : n = 33, r = - 0.2150, Not significant

SCP Thickness = 648.28 - 1.1 Age

✳ ------ ·
Patella : n = 33, r = -0.4516, p < 0.01

SCP Thickness = 751.07 - 2.0 Age

Figure 4.14 : Graph of subchondral plate (SCP) thickness versus osteochondral junction irregularity (OCJ) in the main study group.

n = 132, r = 0.2665, p < 0.01

OCJ Irregularity = 2.03 + 0.001 SCP Thickness
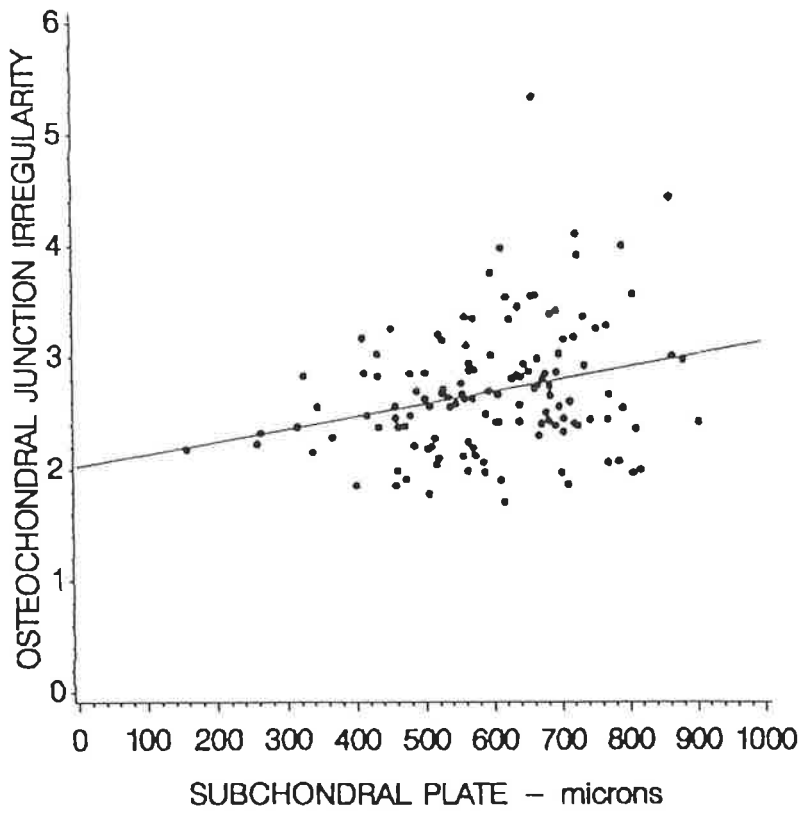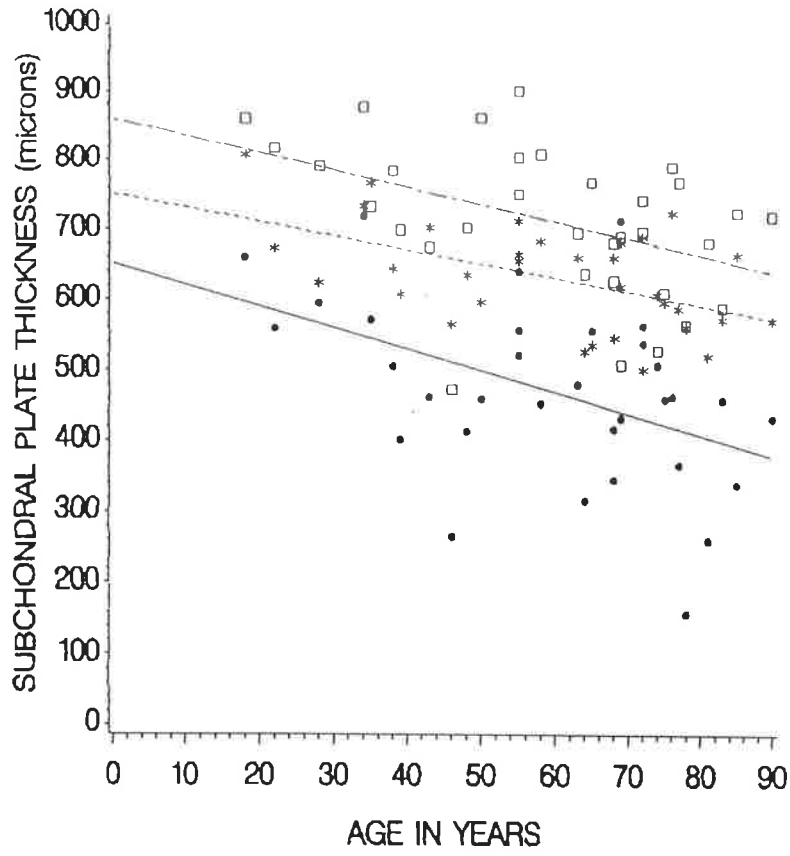
4.6 Calcified Cartilage Thickness

There were no significant differences in the thickness of calcified cartilage between the four regions examined (Table 4.9).

There was no significant correlation between age and the thickness of calcified cartilage. The only significant correlation seen between calcified cartilage thickness and any other parameter from the decalcified blocks was with the irregularity of the osteochondral junction (Figure 4.15) and the irregularity of the tidemark (Figure 4.16). The correlation between calcified cartilage and the irregularity of the osteochondral junction was significant in all regions ($r = 0.5411$ to 0.7981, $p < 0.0001$, $n = 33$ in each case), but the correlation with the irregularity of the tidemark was not significant in any region alone.

4.7 The Irregularity of the Osteochondral Junction

The irregularity of the osteochondral junction was significantly greater in the patella than in any other region (Table 4.10).

There was a significant negative correlation between age and the irregularity of the osteochondral junction (Figure 4.17). This correlation was not significant in any region alone.

A significant positive correlation was seen between the irregularity of the osteochondral junction and the irregularity of the tidemark (Figure 4.18). This correlation was significant only in the medial tibia and trochlea ($r = 0.4187$ and 0.4023 respectively, $p < 0.02$ and $p < 0.01$ respectively, $n = 33$ in both cases).

4.8 The Irregularity of the Tidemark

The irregularity of the tidemark was significantly greater in the trochlea than in either the medial femur or medial tibia, and a significant difference also existed between the patella and medial femur (Table 4.11).

There was no significant correlation between the irregularity of the tidemark and age.

Table 4.9 : Calcified cartilage Thickness

	MIN	25%ile	MEDIAN	75%ile	MAX
MF	69.38	108.26	127.30	148.86	255.35
MT	77.36	117.25	136.67	168.32	242.15
TR	71.77	110.69	137.81	207.52	302.13
PA	87.73	112.60	132.32	169.96	263.56

Multiple Wilcoxon rank tests :

No significant differences between any of the four regions.

Figure 4.15 : Graph of calcified cartilage thickness versus osteochondral junction (OCJ) irregularity in the main study group.

$n = 132, r = 0.5943, p < 0.001$

OCJ Irregularity $= 1.74 + 0.007$ Calcified Cartilage

CALCIFIED CARTILAGE THICKNESS
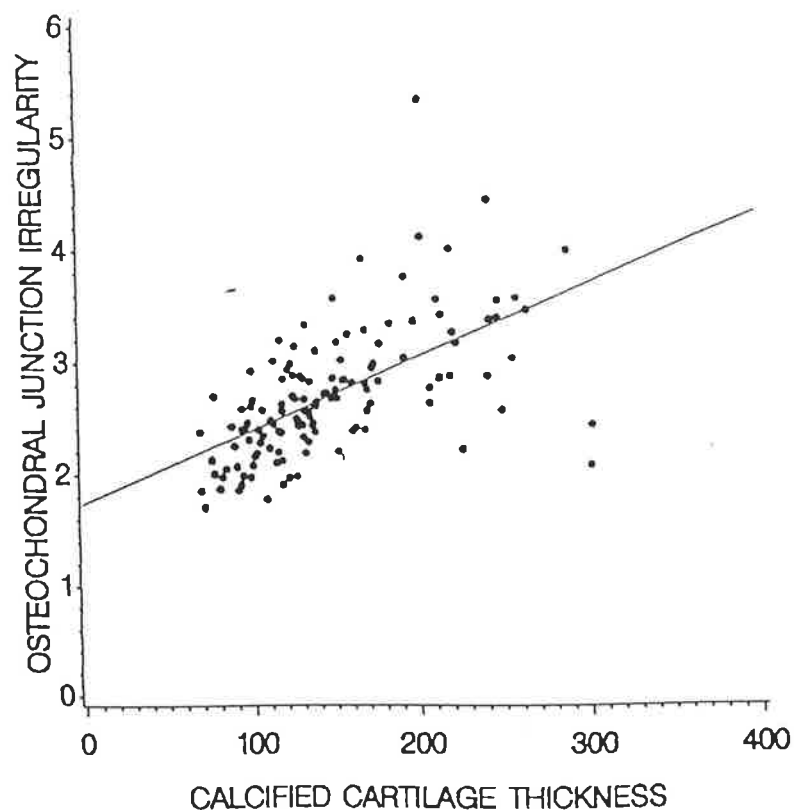
Figure 4.16 : Graph of calcified cartilage thickness versus tidemark irregularity in the main study group.

$$n = 132, r = 0.3424, p < 0.0001$$

Tidemark Irregularity = 1.41 + 0.0008 Calcified Cartilage
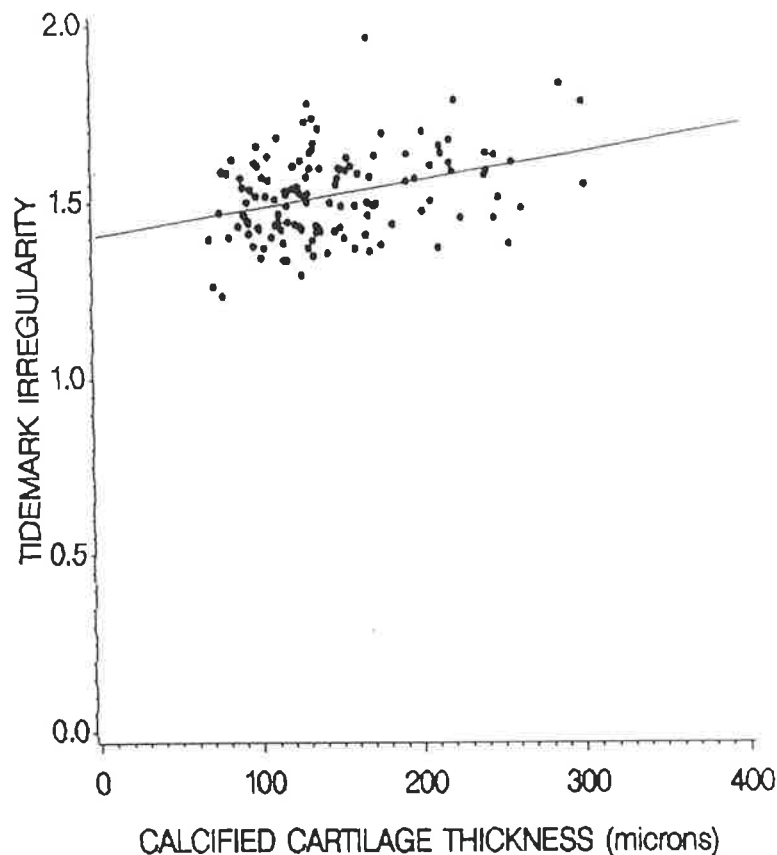
Table 4.10 : Osteochondral Junctions Irregularity (OCJ/TL)

	MIN	25%ile	MEDIAN	75%ile	MAX
MF	1.78	2.19	2.49	2.83	5.34
MT	1.71	2.28	2.58	2.86	4.11
TR	1.91	2.39	2.46	2.86	4.44
PA	1.98	2.65	2.94	3.34	3.92

Multiple Wilcoxon tests :
        The value is significantly greater in the patella than in any other region
(p < 0.006 in all cases)

Figure 4.17 : Graph of age versus osteochondral; junction irregularity in the main study group.

$$n = 132, r = -0.2789, p < 0.01$$

OCJ Irregularity $= 3.20 - 0.01$ Age

Figure 4.18 : Graph of osteochondral (OCJ) junction irregularity versus tidemark irregularity in the main study group

$$n = 132, r = 0.3043, p < 0.0001$$

Tidemark Irregularity $= 1.35 + 0.06$ OCJ Irregularity
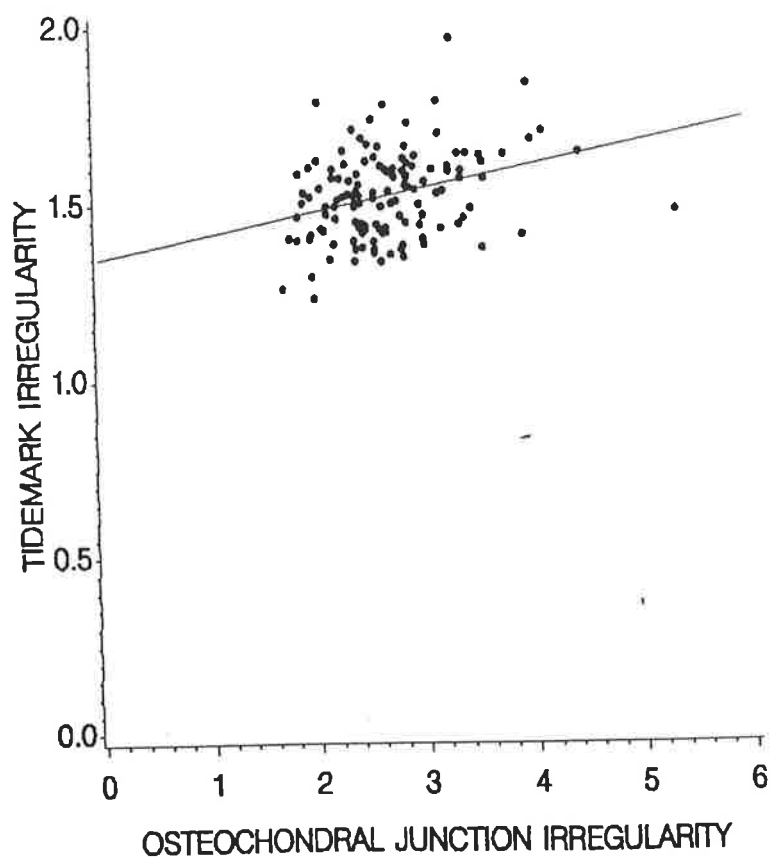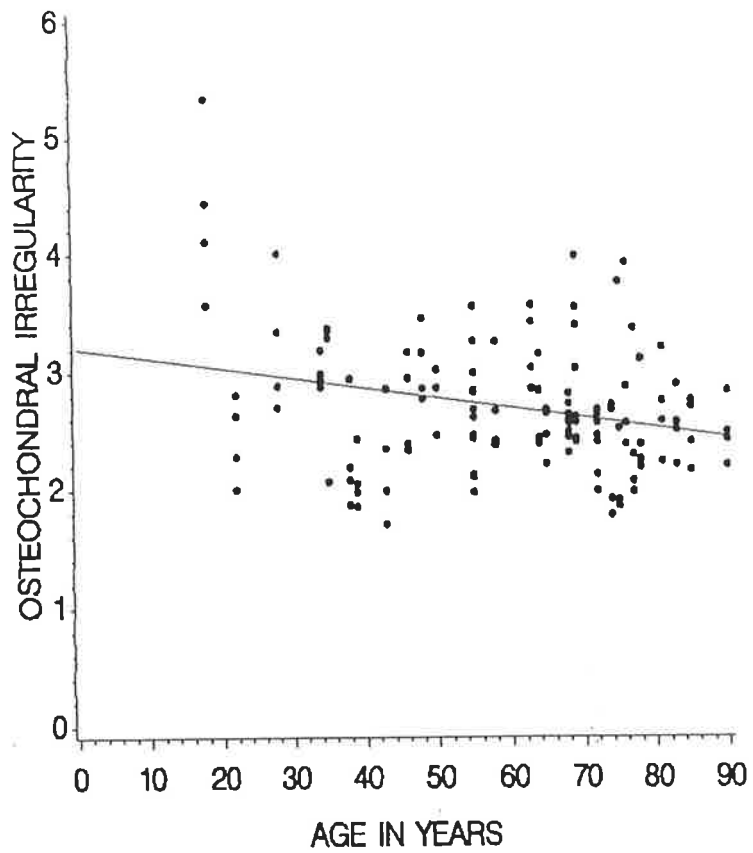
Table 4.11 : Tidemark Irregularity

	MIN	25%ile	MEDIAN	75%ile	MAX
MF	1.30	1.39	1.43	1.53	1.66
MT	1.26	1.53	1.59	1.64	1.84
TR	1.23	1.42	1.50	1.59	1.79
PA	1.37	1.45	1.53	1.60	1.96

Multiple Wilcoxon tests :

The irregularity of the tidemark is significantly greater in the trochlea than in either the medial femur or medial tibia ($p < 0.02$).
The irregularity of the tidemark is also significantly greater in the patella than in the medial femur ($p < 0.05$).

DISCUSSION

Although previous work has examined individual features at the bone-cartilage interface [14,48,56,68,69, 85,97,101,116,117,135,153], this is the first study to examine such a number of these features at one time and to utilise image analysis techniques to quantitate total cartilage thickness, calcified cartilage thickness, subchondral plate thickness, as well as tidemark and osteochondral junction irregularity in opposing articular surfaces, in two separate joints in a large, essentially normal population.

The Mankin score is a semi-quantitative measure of cartilage condition and it is not entirely surprising that it does not reflect the wide regional variation in cartilage condition that was found in Chapter 3, although a gradual deterioration in cartilage condition with increasing age was seen. Examination of the graph of age versus Mankin score (Figure 4.2), however, shows that although not statistically significant, the patella does have a higher Mankin score than the other regions at all ages. The failure of the Mankin scores to display the statistically significant regional differences in cartilage condition seen in Chapter 3 is due to the fact that the assessments of Mankin score were made on single histological blocks from each articular region. In the previous chapter the relatively focal nature of advanced forms of cartilage change was illustrated and single histological blocks may not be truly representative. It is interesting to note that the nett increase in Mankin score with age appear similar in all regions; thus the variable factor between articular regions is the time at which cartilage changes commence. The progression of cartilage changes with age is the same within the four regions examined and appears unaffected by regional differences in functional demands.

The mean value for cartilage thickness obtained in this study (2.58 $\pm$ 1.1 millimetres) appears similar to that obtained previously by Stockwell [133] who found femoral condylar cartilage to be 2.26 $\pm$ 0.49 millimetres thick. Using the

technique of stereophotogrammetry, values for cartilage thickness similar to those seen here have been found in the medial tibia, patella and femur [5].

Cartilage plays an important role in the ability of a joint to deal with loading since it has a degree of elasticity by which potentially damaging forces can be absorbed [147] and because it is able to deform when compressed, cartilage acts to spread loads over a larger area and thus minimise the compressive stresses in the underlying bone [112]. The thicker cartilage is, the better able it is to deform with compression, and the larger the area over which loads are transmitted [38]. A number of experiments have found cartilage thickness to be related to functional demand, in that areas with higher loading have thicker cartilage [97]. Simon [128] found cartilage thickness was not directly related to the compressive forces acting across a joint, but could not exclude the possibility that dynamic or non-compressive forces influenced cartilage thickness.

If cartilage thickness is taken as an indicator of the forces acting upon a joint, the results obtained in this study indicate that the functional demands on the patellofemoral joint, are greater than in the medial tibiofemoral joint. This is surprising since the loading forces transmitted through the patellofemoral joint, during most normal activities, are lower than those transmitted through the medial compartment of the tibiofemoral joint [123]. The areas over which such forces are transmitted are similar: the contact area in the patellofemoral joint has been calculated to range from 2.95 to 5.0 square centimetres [3], and the mean contact area within the medial compartment of the tibiofemoral joint has been calculated to be 4.68 square centimetres [62]. Cartilage within the tibiofemoral joint is, however, protected by the presence of the menisci which transmit 45% of the load across the joint [66,126] and decrease the functional demands on the cartilage. Thus, the cartilage on the medial femur and medial tibia is the thinnest of the regions of the knee examined. It is possible that shear forces may be important in determining cartilage thickness, and, since the patellofemoral joint is exposed to a greater

proportion of shear forces than the tibiofemoral joint, the thickness of the cartilage in the patella and trochlea can be explained.

There is a significant decrease in cartilage thickness throughout the knee with increasing age, which takes place most rapidly in the patella (Figure 4.9). This correlation has been described before by Meachim et al [86] who considered that such thinning was the result of degeneration and fibrillation rather than an age-related shrinkage of otherwise normal cartilage. The decrease in cartilage thickness seen in this study is undoubtedly related to progressive fibrillation, as can be seen by the significant correlation found between cartilage thickness and Mankin score (Figure 4.3). In a radiological study of cartilage thickness in the femoral condyles [50], the correlation between age and cartilage thickness was of only borderline significance, whereas in the current study 17% of the variability in cartilage thickness was accounted for by age. The difference in findings may be related to the different techniques used, as the measurements made in the study by Hall and Wyshak [50] were taken from x-rays with degrees of magnification ranging from 25 to 40 percent, but even so within this study 83% of the variability in cartilage thickness is still unaccounted for, and factors other than age such as functional demands, biochemical and inherited factors and trauma may be involved.

Subchondral plate thickness shows significant variation between the four regions examined and is thickest in the medial tibial plateau. The density of the subchondral plate in this region was also noted by Clark and Huber in their ultrastructural study of the bone-cartilage interface [21]. The thickness of the subchondral plate within the medial tibia may reflect the need for added structural support in the mechanically weak concave surface where, unlike a convex surface, loading will act to separate the structural elements [127]. The thickness of the subchondral plate is significantly lower in the trochlea, which, although also a concave surface is not directly weight-bearing and therefore does not require the bolstering of the subchondral plate seen in the tibia.

Subchondral plate thickness decreases with age in all regions examined except the trochlea (Figure 4.13), and this may reflect the age-related bone loss seen in the trabecular network [92]. A significant correlation was seen between the thickness of the subchondral plate and the irregularity of the osteochondral junction (Figure 4.14). This may simply reflect the fact that the osteochondral junction forms part of the border of the subchondral plate. The significant correlation between subchondral plate thickness and tidemark numbers (Figure 4.7) may be a result of both factors being related to age.

Subchondral plate thickness showed a significant positive correlation with total cartilage thickness (Figure 4.10). This is not surprising since both tissues are known to respond to functional demands [96,139], and both have been shown in this study to be significantly related to age. It is , however, interesting that the region with the thickest cartilage is the trochlea, whilst the tibia is the region with the thickest subchondral plate. It can be said, therefore, that the factors which influence bone and cartilage formation are quite different. This would be expected since the two tissues have very different functions even though both have a role to play in the absorption of the potentially damaging forces that act across a joint.

As blood vessels enter the calcified cartilage and begin to form bone they will simultaneously alter the profile of the bone-cartilage interface, thus the irregularity of the osteochondral junction correlates with the number of focal contacts (Figure 4.6). The irregularity of the osteochondral junction acts to increase the adherence of cartilage to bone by modifying the shear forces acting in this region into compressive ones [25,26]. Such shear forces are high in the patella because of the wide range of movement of the patella across the trochlea and femoral condyles during normal flexion of the knee, and this explains the fact that this is the region with the greatest irregularity of the osteochondral junction.

In this study, the thickness of calcified cartilage was found to range from 69.38 to 302.13 microns, with a mean value of 146.95 ± 52.3 microns. The mean thickness of calcified cartilage in the patella was 148.32 ± 50.3 microns. These values are comparable to previous studies which have found the thickness of calcified cartilage to range from 20 to 230 microns in the femoral head [97] and to have a mean value of 134 microns in the patella [48].

In the current study, as in that of Green et al [48], the thickness of calcified cartilage was not found to vary with age or to change with the condition of the hyaline layer. In contrast, Lane and Bullough [68], in a study of both femoral and humeral heads, found that there was a significant decrease in the thickness of the calcified layer in both males and females with increasing age. These anomalies may be related to differences in technique since Green et al [48] used a microradiographic method, whilst Lane and Bullough [68] used histological techniques and measured the thickness of calcified cartilage using a reference grid eyepiece. Measurements by this latter method would be complicated by the very irregular border of the calcified layer where it adheres to bone. The Quantimet image analysis system used in the present study has undoubted technical advantages, being able to incorporate all elements of calcified cartilage within the section into calculation of thickness and thus obtain a value more representative of the region examined. The study of Muller-Gerbl et al [97], which utilised similar image analysis techniques to those used here, did not have a sufficiently large sample to determine the presence of any age-related changes in calcified cartilage thickness.

Previous studies have found the calcified layer to be thicker in stressed, as opposed to non-stressed, regions within the femoral head [68,85,134]; but here no regional variation could be seen, although comparisons were made between different articular surfaces rather than between different areas within the same articular surface. Muller-Gerbl et al [97] and Oegema et al [101] found there was a significant correlation between calcified and non-calcified cartilage thickness, but this has not been confirmed in the current study. This discrepancy may be explained

by the fact that the calcified cartilage thickness varies widely within one joint ranging from a few microns to 1.5 millimetres [93], and there are also wide differences between individuals [97] and in the current study there is pooled data from four different regions of 33 subjects.

The increase in the number of tidemarks seen with age [13,48,68] has been confirmed by the present study. This increase has been proposed to be an indicator of episodes of reactivation of the calcification front. If this is so, it would be expected that with continued episodes of calcification of the hyaline cartilage, the thickness of the calcified cartilage would increase with age, but this is not the case as calcified cartilage thickness remains unchanged during life. It would appear therefore that as hyaline cartilage undergoes calcification at the tidemark the calcified cartilage is concurrently remodelled, presumably by the action of focal contacts as they lay down bone at the subchondral plate. If the role of calcified cartilage is to provide a transition zone between cartilage and bone and to enhance the binding between these areas [48,68], there may well be an optimal thickness for the calcified layer. If calcified cartilage is too thin it will be an insufficient anchor for the collagen fibres embedded within in it and which extend into the hyaline layer. If it is too thick, its increased density will compromise the elasticity of hyaline cartilage and its role in the transmission and distribution of loading forces. This optimal thickness of calcified cartilage is maintained by an equilibrium between calcification and remodelling, between the tidemark and the focal contacts, and the forces driving this equilibrium must be profound since the calcified layer remains unaffected by quite severe changes in the overlying hyaline cartilage [7,48].

In addition, the significant correlation between osteochondral junction and tidemark irregularity can only be explained if the two are thought of as indicators of calcification and remodelling activity, working in tandem to maintain the optimal thickness of calcified cartilage. The relationship between calcified cartilage, the tidemark and osteochondral junction may be described as follows: the tidemark is

activated by some as yet unknown mechanism or factor related to loading, for example cartilage breakdown products, and as stresses and cartilage damage are not evenly distributed within a joint, calcification will begin in certain areas before others resulting in an increasingly convoluted tidemark. If this is the case then tidemark irregularity can be considered an indicator of calcification activity which will result in an increase in calcified cartilage thickness. This in turn will stimulate an increase in focal contact numbers as the deeper layers of cartilage become hypoxic, or perhaps as overlying chondrocytes become damaged and fail to produce the proposed cartilage anti-invasion factor. The resulting increase in calcified cartilage remodelling, as part of the continuous low-grade remodelling of the subchondral plate by focal contacts, will ensure that the thickness of the calcified layer does not exceed that which is required for optimum joint function. Osteochondral junction irregularity appears to be a marker for in focal contact numbers and subchondral vascularity, and this is supported by the significant correlation between osteochondral junction irregularity and focal contact numbers (Figure 4.6).

The number of tidemarks is significantly lower in the tibia than in the other regions studied (Table 4.5). This is surprising if reactivation of the calcification front is thought to be a response to stresses experienced by the articular surface, since stresses of a similar magnitude would be expected in the tibial plateau and opposing femoral condyle. The stresses may not, however, be equivalent, if the menisci act to diminish the load transmitted directly to the tibial cartilage surface. Alternatively, the number of tidemarks in the tibia may be similar to those seen in the femur but they are somehow obscured from view: this, however, seems unlikely. Recent work by Revell et al [117] found that, in individuals with multiple tidemarks, more than one may be metabolically active at any time. This work was restricted to femoral heads affected by osteoarthritis and cannot be thought of as representing a normal state of affairs, but it is possible that a similar situation

exists in normal ageing individuals. Any attempt to explain the method and reasons for tidemark duplication are beyond the scope of an histological study, but it can be hypothesized that if tidemark activation is initiated by cartilage degeneration, the cartilage damage seen with increasing age will result in an increase in the stimulation of tidemark activity, and possibly in tidemark duplication.

Some authors have found more focal contacts in areas of high loading within a joint [33,69], but in the current study, where different joints were compared, focal contacts were not more numerous in the tibiofemoral joint which is directly involved in weight bearing. Focal contacts were in fact significantly more numerous in the trochlea than elsewhere, and, as this was also the region with the thickest cartilage, this would support the hypothesis that focal contacts are involved in maintaining cartilage nutrition [29,54,59]. There was, however, no significant correlation between cartilage thickness and focal contact numbers in the total study group, nor was any correlation between focal contacts and age seen, in contrast to previous studies [67,85,153], but this may be due to the non-representative nature of values obtained from a single block. Nor was there any significant correlation seen between subchondral plate thickness and focal contact numbers, arguing against a decrease in focal contact numbers due to thickening of the subchondral plate being a mechanism of cartilage damage [29]. The trochlea is also the area exhibiting the greatest irregularity of the tidemark, suggesting that this is a region with high calcification activity. This finding, combined with the high degree of osteochondral junction irregularity in the patella, suggests that the patellofemoral joint has a high level of activity at the bone-cartilage interface, with greater remodelling of the calcified cartilage and the subchondral bone plate in comparison to the tibiofemoral joint.

The most striking finding in this study was the constancy of calcified cartilage thickness in the knee. It does not vary with age or region, unlike the total

cartilage thickness or the thickness of the subchondral plate. Such findings suggest an active process to maintain calcified cartilage thickness at an optimum level. The results suggest that the constancy of the calcified layer is the result of the tidemark and focal contacts acting in a coordinated manner, the tidemark forming the calcified layer and the focal contacts remodelling it.

The patellofemoral joint has been shown, in Chapter 3, to be more widely and severely affected by age-related cartilage changes than the medial tibiofemoral joint. The examination of the structures at the bone-cartilage interface suggest that it is also the joint within the knee with the greatest degree of remodelling of calcified cartilage and the subchondral plate.

The nature of this relationship between cartilage degeneration and remodelling of the bone-cartilage interface is unclear. It may be that active calcification, focal contact ingrowth and the remodelling of both calcified cartilage and the subchondral bone plate may all be secondary to initial changes in cartilage condition and thus represent attempts at repair. This hypothesis cannot be disproved by the current study.

It may be, however, that as suggested by Bullough [13], there is a continuous low-grade remodelling and growth of long bones throughout life and if this is mediated by focal contacts, it would explain why they do not disappear once skeletal maturity is achieved. This continuous remodelling may lead to changes in joint geometry and loading and may eventually result in cartilage damage [13]. The fact that a disease such as osteoarthritis, where there is widespread cartilage damage in association with great variability and thinning of calcified cartilage [93] and thickening of the subchondral plate [22,28] supports the hypothesis that this disease results from and imbalance in the tidemark and focal contact equilibrium which maintains an optimal calcified cartilage thickness, and would argue against the association between cartilage condition and activity at the bone-cartilage interface being coincidental. A possible model for osteoarthritis would thus involve a failure of normal tidemark activity so that, although there is continued remodelling of the

calcified layer and bone formation by focal contacts with a consequent increase in subchondral plate thickness, there is no reactivation of calcification of hyaline cartilage at the tidemark, resulting in a thinner calcified layer. This would result in the collagen fibres of hyaline cartilage no longer being firmly anchored, rendering it susceptible to disruption by shearing forces.

The current work suggests that differences in the degree of age-related changes within the regions of the knee may be related to differences in the activity of the bone-cartilage interface, but that calcified cartilage thickness *per se* does not have a role in the development of age-related changes. Other possible mechanisms of cartilage damage that have been proposed, such as changes in the density of the cancellous bone and the presence of trabecular microfractures, must be studied before the bone-cartilage interface can be considered to hold a key to the development of cartilage damage.

CONCLUSIONS

1. Cartilage condition as assessed by Mankin score does not show any significant regional variation, although the Mankin score does increase significantly with age. The failure to repeat the regional differences in cartilage condition seen in Chapter 3 may be due to the non-representative nature of the blocks used for Mankin score assessment.

2. Total cartilage thickness decreases significantly with age, as a result of degenerative changes in all regions of the knee and most markedly in the patella.

3. Subchondral plate thickness is greatest in the tibia, in order to bolster the mechanically weak concave surface. A significant decrease in subchondral plate thickness is seen in all regions of the knee with increasing age, except the trochlea, and this reflects the decrease in bone volume seen throughout the skeleton with increasing age.

4. Calcified cartilage thickness appears as a constant, showing no regional variation or any changes with age. This is despite a significant increase in tidemark numbers with age.

5. It is proposed that there is an optimum thickness of calcified cartilage, at which collagen fibres are firmly anchored, without adversely affecting the elasticity of the overlying hyaline cartilage and its ability to absorb potentially damaging impulse loading forces.

6. An equilibrium between tidemark and focal contact activity is proposed as the mechanism by which this optimum calcified cartilage thickness is maintained.

7. The greatest degree of tidemark and focal contact activity appears to be in the patellofemoral joint, which has already been shown to be an area of greater age-related cartilage change, suggesting that the bone-cartilage interface has a role in the development of such cartilage changes.

8. It is proposed that abnormalities in this equilibrium predispose to cartilage damage in diseases such as osteoarthritis.

CHAPTER 5 : HISTOQUANTITATION OF SUBCHONDRAL BONE

The patellofemoral joint has already been shown to be more severely affected by age-related cartilage changes than the other regions of the knee, and in the previous chapter, it has also been shown to be an area of greater remodelling activity at the bone-cartilage interface, suggesting this area has a role in the development of cartilage changes. Previous work, however, has concentrated on the role of subchondral cancellous bone in the development of cartilage damage following the work of Radin et al [111,112], who demonstrated the important role bone plays in the ability of a joint to absorb potentially damaging impulse forces. It is possible, therefore, that the regional differences in cartilage condition within a normal ageing population may be the result of differences in the structure and compliance of the cancellous bone. In order to explore this possibility, undecalcified blocks were obtained from the central areas of the medial femoral condyle, medial tibial facet, trochlea and patella. Histoquantitation was performed using the Quantimet 520 Image Analysing System at 10 times objective magnification. Values were obtained for percent bone volume (BV/TV), total surface (BS/TV) in mm^2/ mm^3, and trabecular thickness (Tb.Th) and trabecular spacing (Tb.Sp) both in micrometers. As a result of difficulties in processing, blocks were obtained from all four regions in only 31 of the 33 individuals in Group 1.

RESULTS

The mean values obtained for each parameter from the main study group can be seen in Table 5.1. There are no significant gender related differences (Table 5.2), but significant left-right differences exist for age and for BS/TV (Table 5.3).

Table 5.1 : Bone histoquantitation parameters for the main study group n=124. Values given as mean ± standard deviation

Age (years)	57.90 ± 18.6
BV/TV %	30.60 ± 7.0
BS/TV (mm^2/mm^3)	5.71 ± 1.0
Tb.Th (microns)	109.74 ± 24.7
Tb.Sp (microns)	256.94 ± 57.3

Table 5.2 : Bone histoquantitation parameters for males and females within the main study group. Values given as mean ± standard deviation

	Males n = 76	Females n = 48	p
AGE	57.74 ± 17.7	58.17 ± 20.1	N.S.
BV/TV	31.35 ± 7.0	29.40 ± 6.8	N.S.
BS/TV	5.76 ± 1.1	5.62 ± 0.8	N.S.
Tb.Th	111.78 ± 24.3	106.51 + 25.1	N.S.
Tb.Sp	253.86 ± 60.0	261.81 ± 52.9	N.S.

Table 5.3 : Bone histoquantitation data from right and left knees in the main study group. Values given as mean ± standard deviation.

	Right n = 56	Left n = 68	p
AGE	52.29 ± 17.6	62.53 ± 18.1	<0.01
BV/TV	30.48 ± 6.93	30.69 ± 7.1	N.S.
BS/TV	5.50 ± 1.0	5.88 ± 1.0	<0.05
Tb.Th	113.82 ± 27.3	106.39 ± 21.9	N.S.
Tb.Sp	267.21 ± 57.7	248.50 ± 55.9	N.S.

5.1 Percent Mineral Bone - BV/TV

BV/TV was significantly higher in the patella than in any other region of the knee (Table 5.4). The BV/TV of sections taken from the medial tibial plateau were not significantly different to those from the medial femur on paired t-testing (p > 0.10) and the two values showed a significant correlation (Figure 5.1). Similarly, although the BV/TV of sections from the trochlea was significantly less then that from the patella on paired t-testing (p < 0.0001), the two regions exhibited a significant positive correlation (Figure 5.2).

A negative correlation between age and BV/TV was significant in the main study group (Figure 5.3), and in females alone, but not in males (Figure 5.4). The correlation with age was significant in all regions of the knee except the patella (Figure 5.5).

BV/TV and BS/TV exhibited a positive non-linear correlation in the main study group (Figure 5.6), and in males, but not in females (Figure 5.7), and in the medial femoral condyle and medial tibial plateau, but not elsewhere (Figure 5.8).

There was a significant positive correlation between BV/TV and Tb.Th in the main study group (Figure 5.9), and this correlation was significant in both sexes and in all four regions examined (Figures 5.10 and 5.11).

A non-linear negative correlation was seen between BV/TV and Tb.Sp in the main study group (Figure 5.12), and this also was significant in both sexes and in all four regions of the knee (Figures 5.13 and 5.14).

5.2 Total Surface - BS/TV mm^2/ mm^3

BS/TV was significantly higher in the trochlea than in either the medial femur or medial tibia (Table 5.5). There was no significant correlation of BS/TV with age (r = 0.1234, p > 0.10, n = 124).

There was no significant difference in the values of BS/TV between either the medial femur and medial tibia, or the trochlea and patella on paired t-testing. A significant positive correlation existed between the BS/TV of the medial femoral

Figure 5.1 : Graph of the BV/TV in the medial femur versus the BV/TV in the medial tibia.

r = 0.6258, p = 0.0001, n = 31

BV/TV Tibia = 4.03 + 0.9 BV/TV Femur

Figure 5.2 : Graph of BV/TV in the patella versus BV/TV in the trochlea.

r = 0.4169, p = 0.0196, n = 31

BV/TV Trochlea = 13.81 + 0.4 BV/TV Patella

Table 5.4 : % BV/TV in the four regions of the knee. n = 31 in each region. Mean value $\pm$ Standard Deviation (S.D.)

Region	Mean $\pm$ S.D.
Medial Femur	28.51 $\pm$ 5.3
Medial Tibia	30.77 $\pm$ 7.2
Trochlea	27.63 $\pm$ 6.4
Patella	35.49 $\pm$ 6.4

Multiple t-tests : BV/TV is significantly greater in the patella than in any other of the regions (p < 0.009 in all cases). There are no other significant differences.
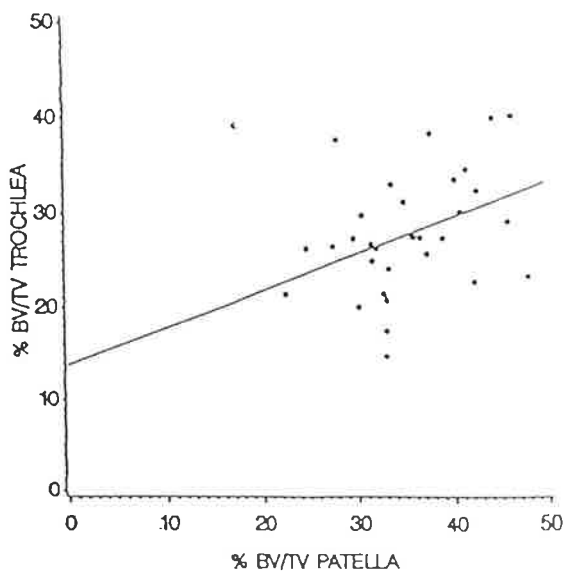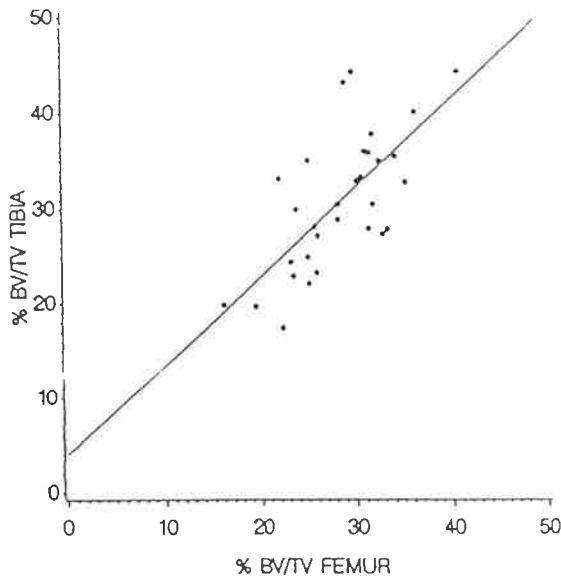
Figure 5.3 : Graph of age in years versus BV/TV (% bone volume).

$r = -0.3156$, $p < 0.0005$, $n = 132$

$BV/TV = 37.46 - 0.12$ Age

Figure 5.4 : Graph of age versus BV/TV (% bone volume) in males and females.

Males : $r = -0.2150$, $n = 74$, Not significant

$BV/TV = 36.28 - 0.09$ Age

O — — Females : $r = -0.4467$, $p < 0.01$, $n = 48$.

$BV/TV = 38.30 - 0.16$ Age

Figure 5.5 : Graph of age versus BV/TV (% bone volume) in the four regions of the knee.

● — Medial Femur : $r = -0.3967$, $p < 0.03$, $n = 31$

$BV/TV = 35.02 - 0.11$ Age

□— · — Medial Tibia : $r = -0.4626$, $p < 0.01$, $n = 31$

$BV/TV = 40.99 - 0.18$ Age

O — — Trochlea : $r = -0.3589$, $p < 0.05$, $n = 31$

$BV/TV = 34.65 - 0.12$ Age

Patella : $r = -0.1883$, $n = 31$, Not significant

$BV/TV = 39.19 - 0.06$ Age
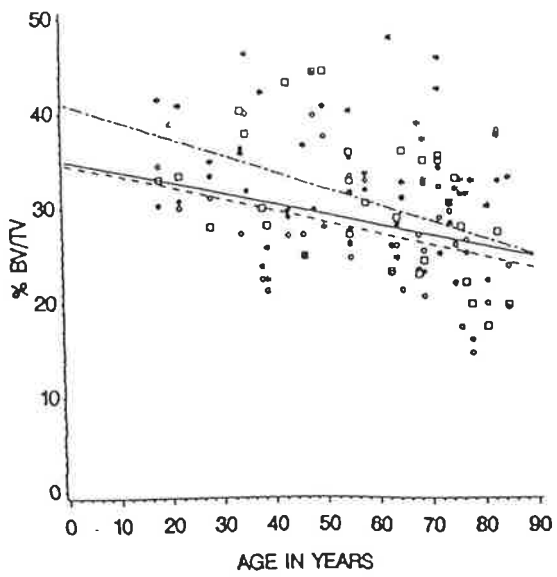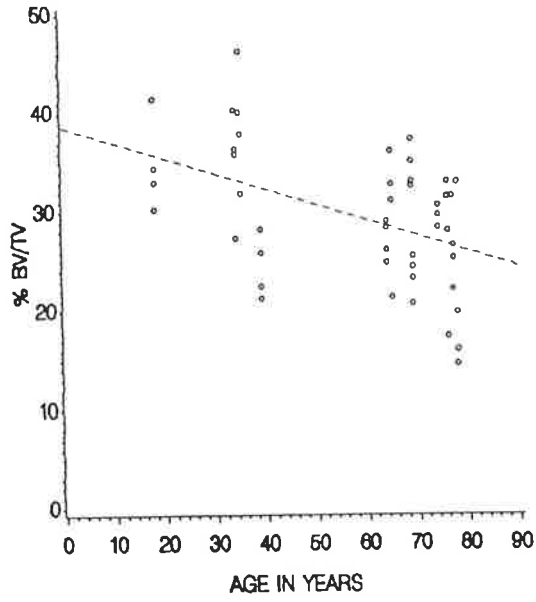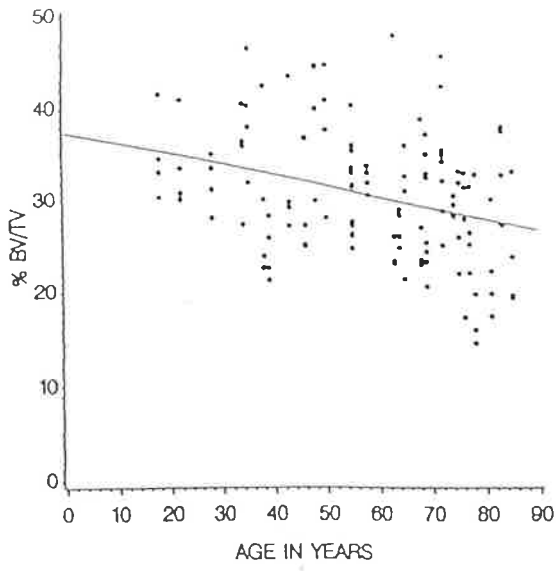
Figure 5.6 : Graph of BV/TV versus BS/TV for the total study group.

$r = 0.4012$, $p < 0.0001$, $n = 132$

$BS/TV = 2.14 \, BV/TV^{0.3}$

Figure 5.7 : Graph of BV/TV versus BS/TV by gender.

Males : $r = 0.4761$, $p < 0.0001$, $n = 76$

$BS/TV = 1.55 \, BV/TV^{0.4}$

Females : $r = 0.2382$, $n = 48$, Not significant

$BS/TV = 3.44 \, BV/TV^{0.15}$

Figure 5.8 : Graph of BV/TV versus BS/TV in the medial femoral condyle and medial tibial plateau.

Medial Femur : $r = 0.4046$, $p < 0.05$, $n = 31$

$BS/TV = 1.9 \, BV/TV^{0.3}$

Medial Tibia : $r = 0.7216$, $p < 0.0001$, $n = 31$

$BS/TV = 0.6 \, BV/TV^{0.7}$

Trochlea : $r = 0.3183$, $n = 31$ Not significant

$BS/TV = 3.2 \, BV/TV^{0.2}$

Patella : $r = 0.2331$, $n = 31$ Not significant

$BS/TV = 2.9 \, BV/TV^{0.2}$
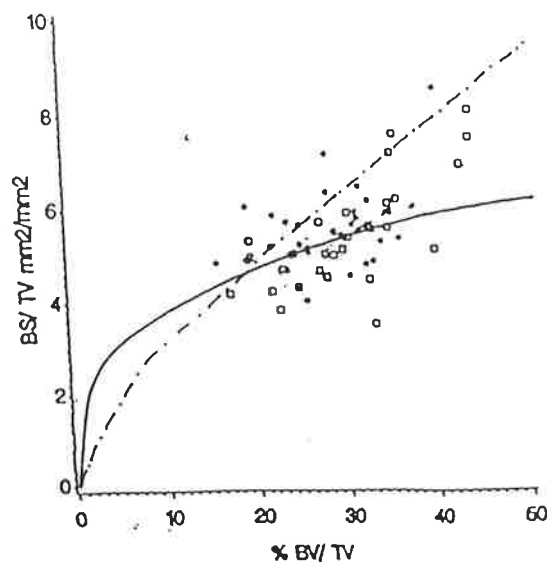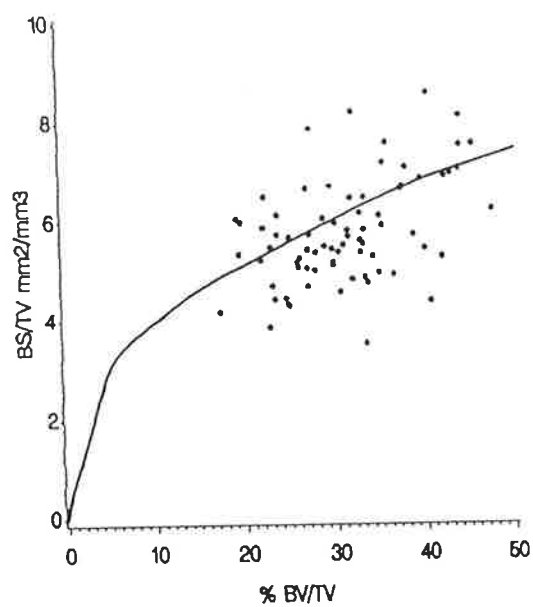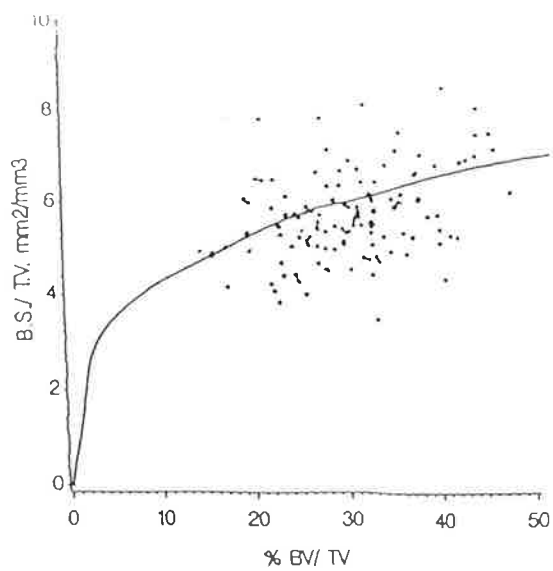
Figure 5.9 : Graph of BV/TV versus trabecular thickness in the main study group.

r = 0.7138, p < 0.0001, n = 124

Tb.Th = 32.45 + 2.5 BV/TV

Figure 5.10 : Graph of BV/TV versus trabecular thickness by gender.

● —— Males : r = 0.6373, p < 0.0001, n = 74

Tb.Th = 42.38 + 2.21 BV/TV

○ — — Females : r = 0.8263, p < 0.0001, n = 48

Tb.Th = 17.00 + 3.0 BV/TV

Figure 5.11 : Graph of BV/TV versus Tb.Th by region.

● —— Medial Femur : r = 0.6551, p < 0.0001, n = 31

Tb.Th = 33.85 +2.5 BV/TV

□ — · — Medial Tibia : r = 0.5092, p < 0.0100, n = 31

Tb.Th = 66.44 + 1.6

○ — — Trochlea : r = 0.8100, p < 0.0001, n = 31

Tb.Th = 21.41 + 2.6 BV/TV

✳ ····· Patella : r = 0.6870, p < 0.0001, n = 31

Tb.Th = 30.43 + 2.7 BV/TV
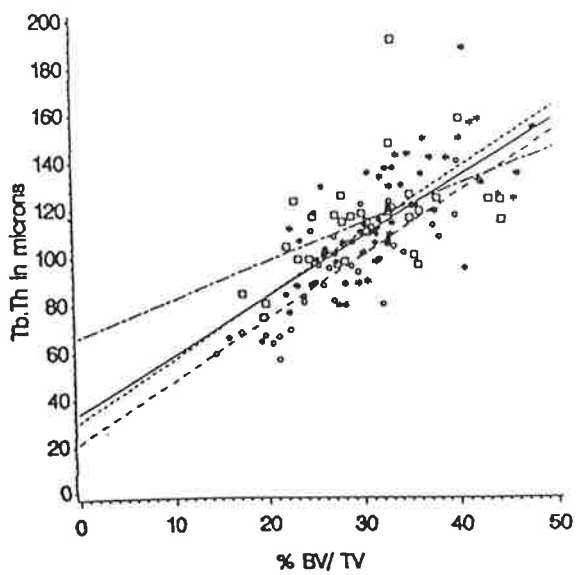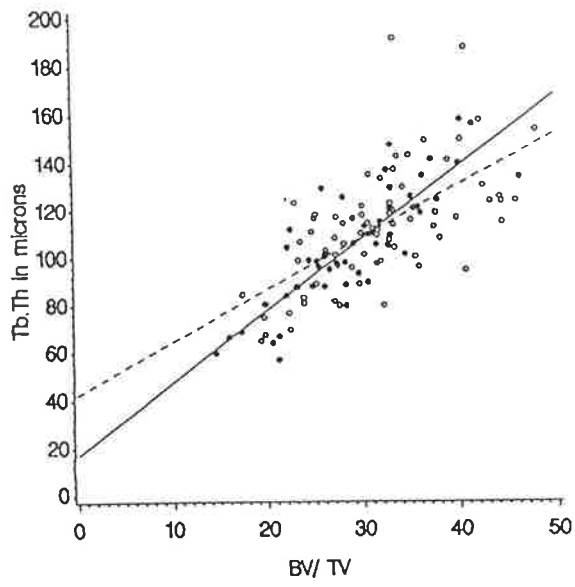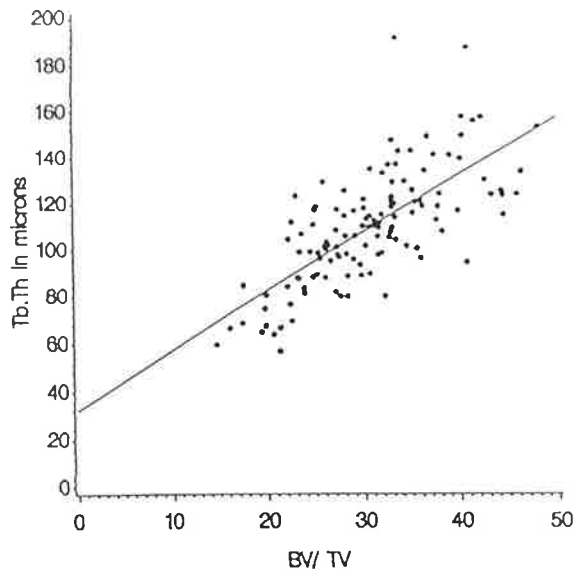
Figure 5.12 : Graph of BV/TV versus Tb.Sp in the main study group.

$$r = -0.7151, p < 0.0001, n = 124$$

$$Tb.Sp = 2.08 \; BV/TV^{-0.6}$$

Figure 5.13 : Graph of BV/TV versus Tb.Sp by gender

●—— Males : $r = -0.7296, p < 0.0001, n = 76$

$$Tb.Sp = 3.03 \; BV/TV^{-0.7}$$

○— — — Females : $r = -0.6878, p < 0.0001, n = 48$

$$Tb.Sp = 1.48 \; BV/TV^{-0.5}$$

Figure 5.14 : Graph of BV/TV versus Tb.Sp by region.

●—— Medial Femur : $r = -0.6817, p < 0.0001, n = 31$

$$Tb.Sp = 1.68 \; BV/TV^{-0.6}$$

□—·— Medial Tibia : $r = -0.8371, p < 0.0001, n = 31$

$$Tb.Sp = 4.45 \; BV/TV^{-0.8}$$

○— — Trochlea : $r = -0.7403, p < 0.0001, n = 31$

$$Tb.Sp = 1.52 \; BV/TV^{-0.6}$$

✳---- Patella : $r = -0.6788, p < 0.0001, n = 31$

$$Tb.Sp = 3.27 \; BV/TV^{-0.7}$$
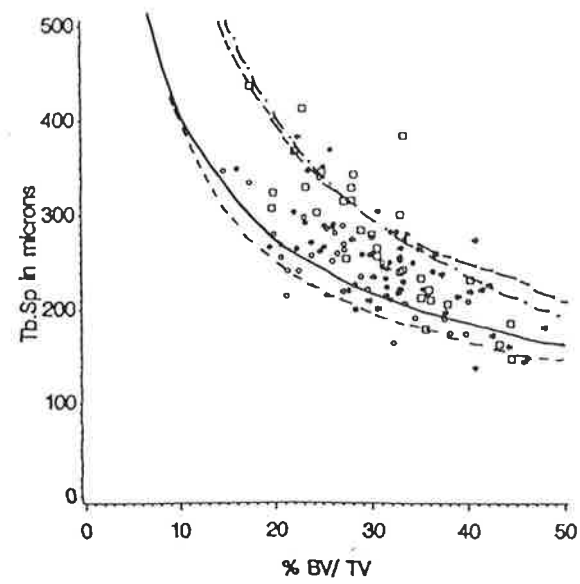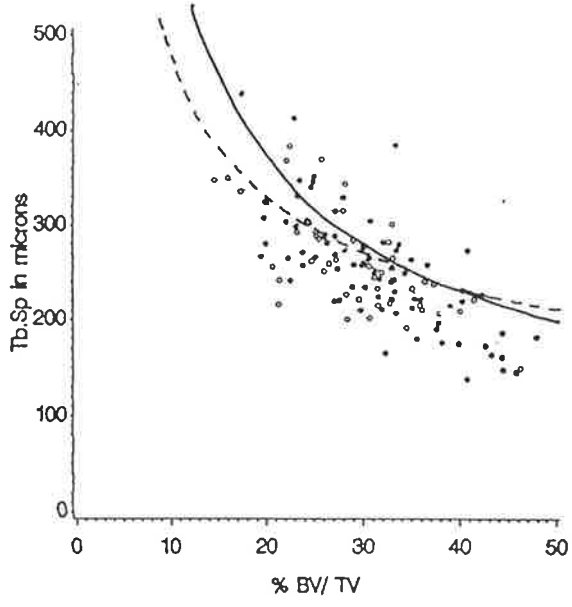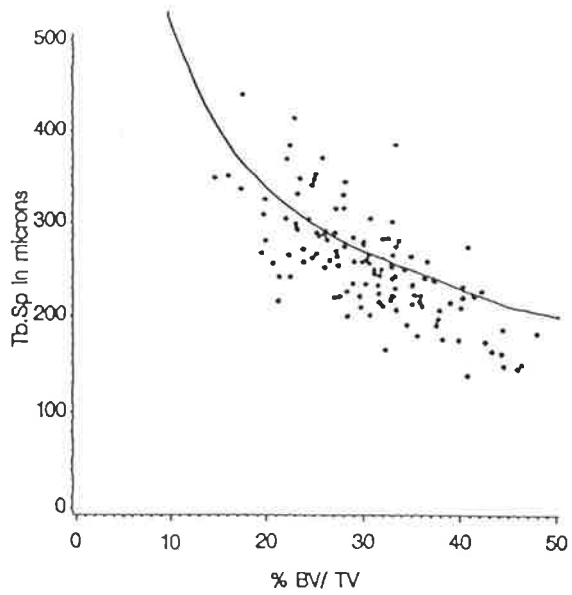
Table 5.5 : BS/TV for each region within the knee. n = 31 for each region.

Region	Mean ± S.D.
Medial Femur	5.53 ± 0.9
Trochlea	5.99 ± 0.9
Medial Tibia	5.42 ± 1.1
Patella	5.88 ± 0.9

Multiple t-tests : BS/TV is signifcantly greater in the trochlea than in the medial femur (p < 0.05) or medial tibia (p < 0.03).

Figure 5.15 : Graph of the BS/TV of the medial femur versus the BS/TV of the medial tibia.

r = 0.4952, p < 0.01, n = 31

BS/TV Tibia = 1.54 + 0.7 BS/TV Femur
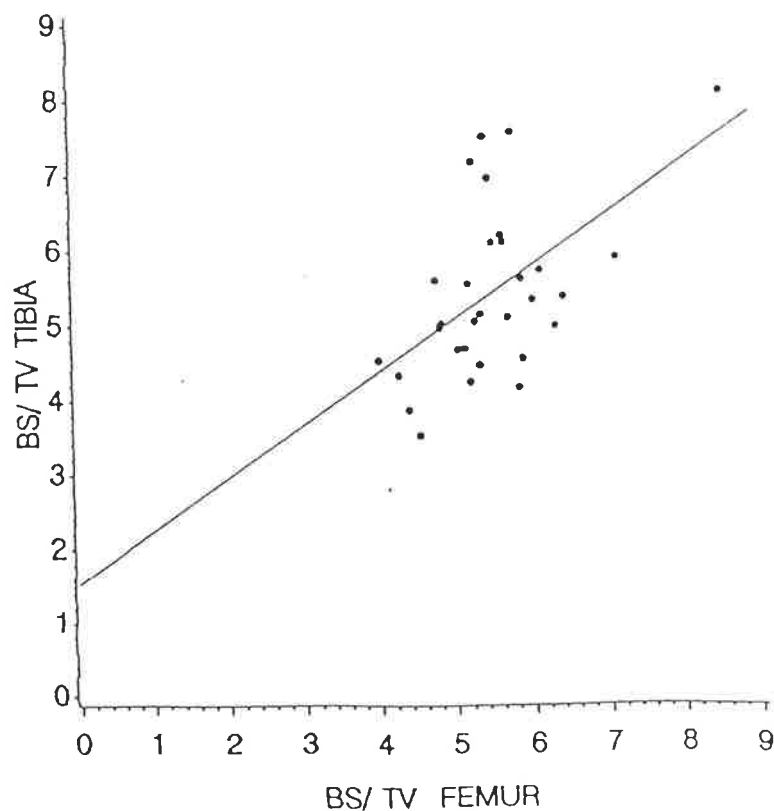
condyle and of the medial tibial plateau (Figure 5.15), but this correlation was not significant between the patella and trochlea (r = 0.1224, p > 0.50, n = 31).

The negative correlation between BS/TV and Tb.Th was significant in the main study group and both sexes, but regionally significant only in the medial femoral condyle and patella (Figures 5.16 to 5.18).

A negative non-linear correlation was also seen between BS/TV and Tb.Sp and was significant in the main study group, in both males and females and in all four regions (Figures 5.19 to 5.21).

5.3 Trabecular Thickness - Tb.Th mm

Tb.Th was significantly greater in the patella than in any other region except the medial tibia. Trabeculae were significantly thinner in the trochlea than elsewhere (Table 5.6).

Paired t-testing found a significant difference in the Tb.Th between the patella and trochlea (p < 0.0001), but not between the medial femur and medial tibia. A significant positive correlation was found between Tb.Th in the medial femoral condyle and that in the medial tibial plateau (Figure 5.22), but no significant correlation was found between the patella and trochlea (r = 0.3155, p > 0.05, n = 31).

Tb.Th and age exhibited a negative correlation significant in the main study group, both males and female subgroups and in all regions of the knee (Figure 5.23 to 5.25).

5.4 Trabecular Spacing - Tb.Sp mm

Tb.Sp was significantly greater in the medial femoral condyle and medial tibial plateau than in the patella (Table 5.7).

Paired t-testing found no significant differences in the Tb.Sp between the patella and trochlea, or between the medial tibia and femur. There was no significant correlation of Tb.Sp with age (r = 0.0290, p > 0.70, n = 124).

Figure 5.16 : Graph of BS/TV versus trabecular thickness in the main study group.

$$r = -0.3195, p < 0.001, n = 124$$

$$Tb.Th = 155.96 - 8.1 \ BS/TV$$

Figure 5.17 : Graph of BS/TV versus trabecular thickness by gender.

● —— Males : $r = -0.3428, p < 0.01, n = 76$

$$Tb.Th = 157.00 - 8.0 \ BS/TV$$

○ — — Females : $r = -0.3103, p < 0.05, n = 48$

$$Tb.Th = 158.50 - 9.5 \ BS/TV$$

Figure 5.18 : Graph of BS/TV versus trabecular thickness by region.

● —— Medial Femur : $r = -0.4156, p < 0.05, n = 31$

$$Tb.Th = 157.86 - 9.6 \ BS/TV$$

Medial Tibia : $r = -0.1846, n = 31$, Not significant

$$Tb.Th = 135.20 - 3.7 \ BS/TV$$

Trochlea : $r = -0.2728, n = 31$, Not significant

$$Tb.Th = 133.38 - 6.6 \ BS/TV$$

✳ ----· Patella : $r = -0.5133, p < 0.01, n = 31$

$$Tb.Th = 204.6 - 13.6 \ BS/TV$$
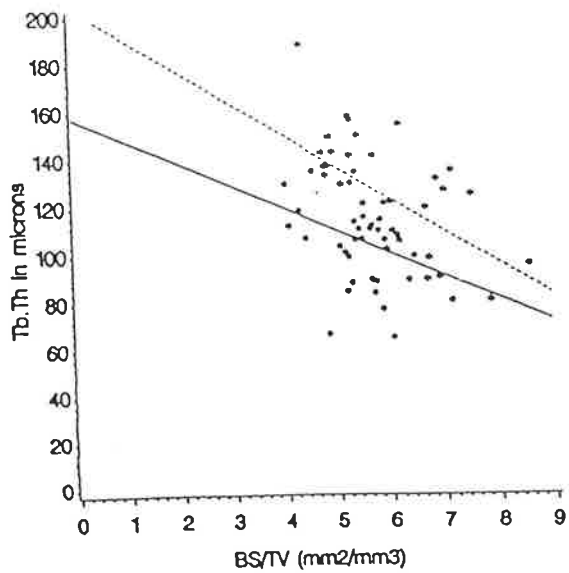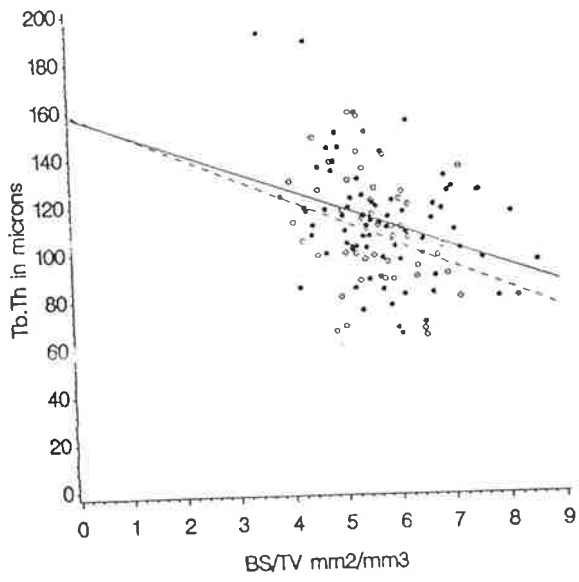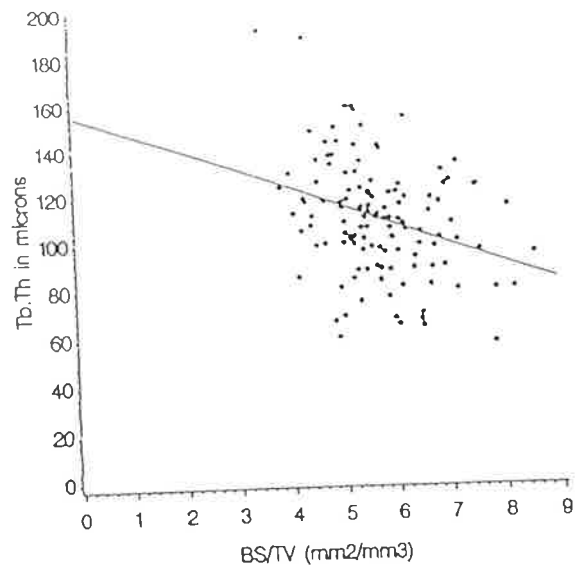
Figure 5.19 : Graph of BS/TV versus trabecular spacing in the main study group.

$r = -0.8655$, $p < 0.0001$, $n = 124$

$Tb.Sp = 1.91 \; BS/TV^{-1.17}$

Figure 5.20 : Graph of BS/TV versus trabecular spacing by gender.

● ——   Males : $r = -0.8761$, $p < 0.0001$, $n = 31$

$Tb.Sp = 1.88 \; BS/TV^{-1.17}$

○ – – –   Females : $r = -0.8421$, $p < 0.0001$, $n = 31$

$Tb.Sp = 1.97 \; BS/TV^{-1.19}$

Figure 5.21 : Graph of BS/TV versus trabecular spacing by region.

● ——   Medial Femur : $r = -0.9016$, $p < 0.0001$, $n = 31$

$Tb.Sp = 1.88 \; BS/TV^{-1.2}$

□ – · —   Medial Tibia : $r = -0.8997$, $p < 0.0001$, $n = 31$

$Tb.Sp = 2.02 \; BS/TV^{-1.2}$

○ – –   Trochlea : $r = -0.8545$, $p < 0.0001$, $n = 31$

$Tb.Sp = 2.11 \; BS/TV^{-1.2}$

✳ ······   Patella : $r = -0.8249$, $p < 0.0001$, $n = 31$

$Tb.Sp = 1.56 \; BS/TV^{-1.1}$
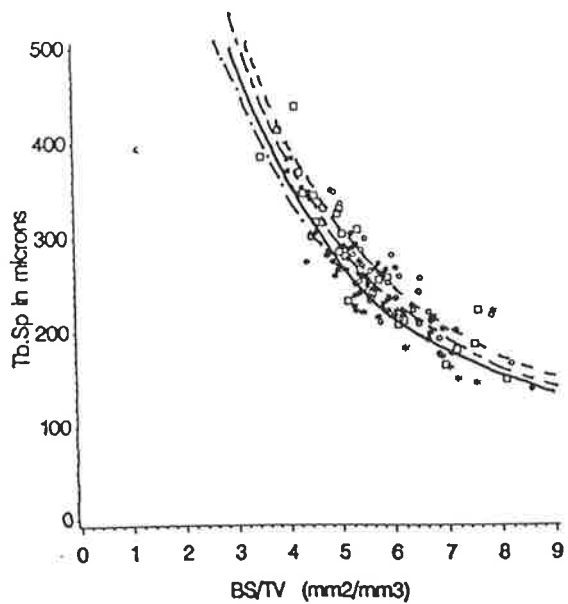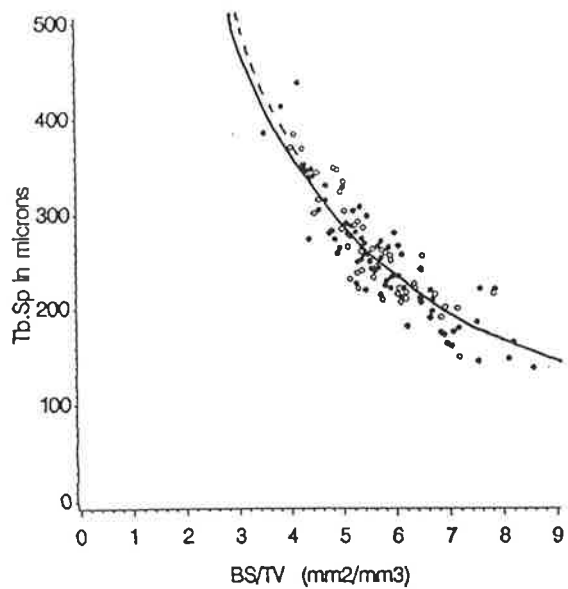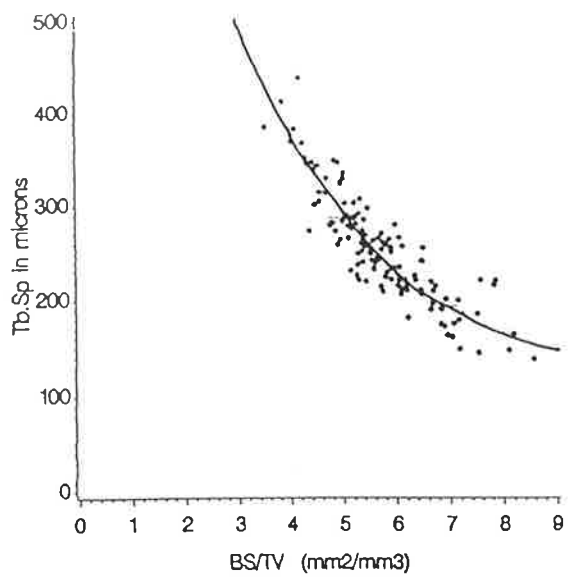
Table 5.6 : Values for trabecular thickness in microns in each region in the main study region. n = 31 in each region.

Region	Mean ± S.D.
Medial Femur	104.67 ± 20.2
Medial Tibia	115.38 ± 22.4
Trochlea	94.07 ± 20.6
Patella	124.85 ± 24.7

Multiple t-tests :   The trabecular thickness is significantly less in the trochlea than in all other regions (p < 0.05).

Trabecular thickness is significanlty greater in the patella than in all other regions except the medial tibia (p < 0.001).

Figure 5.22 : Graph of trabecular thickness in the femur versus trabecular thickness in the tibia.

r = 0.4822, p < 0.001, n = 31

Tb.Th Tibia = 49.39 + 0.6 Tb.Th Femur
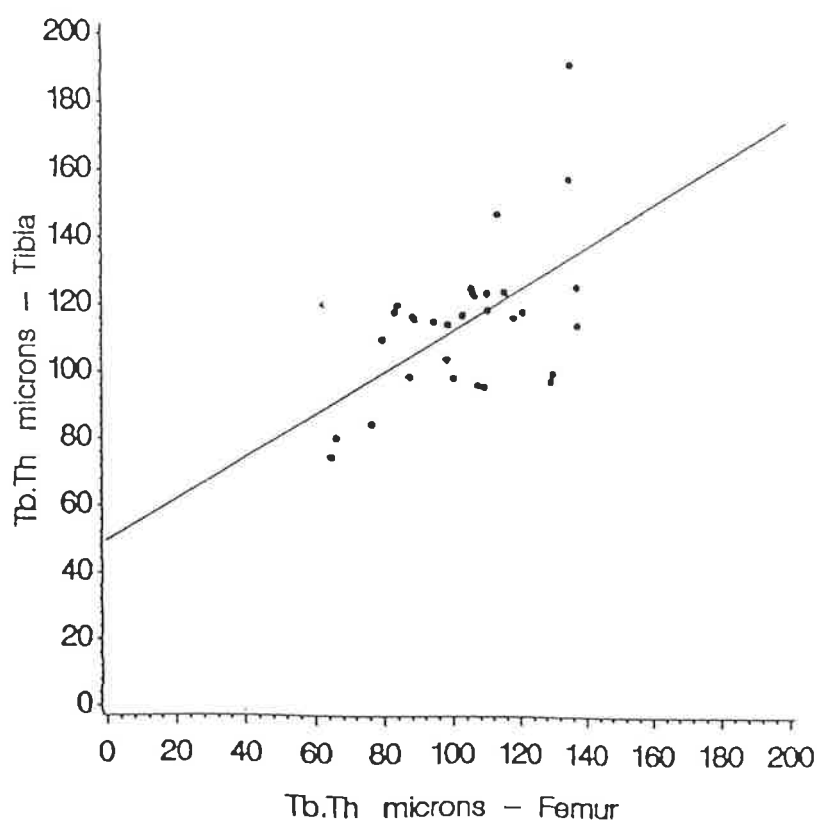
Figure 5.23 : Graph of age versus trabecular thickness in the main study group.

$r = -0.4556, n = 76$

$Tb.Th = 144.82 - 0.61\ Age$

Figure 5.24 : Graph of age versus trabecular thickness by gender.

● ——   Males : $r = -0.4499, p < 0.0001, n = 76$

$Tb.Th = 147.6 - 0.62\ Age$

○ — — —   Females : $r = -0.4670, p < 0.001, n = 48$

$Tb.Th = 140.5 - 0.58\ Age$

Figure 5.25 : Graph of age versus trabecular thickness by region.

● ——   Medial Femur : $r = -0.5851, p < 0.001, n = 31$

$Tb.Th = 141.1 - 0.63\ Age$

□ —·—   Medial Tibia : $r - 0.6666, p < 0.0001, n = 31$

$Tb.Th = 161.4 - 0.79\ Age$

○ — — —   Trochlea : $r = -0.3798, p < 0.001, n = 31$

$Tb.Th = 118.2 - 0.42\ Age$

✳ ······   Patella : $r = -0.4424, p < 0.05, n = 31$

$Tb.Th = 158.6 - 0.58\ Age$
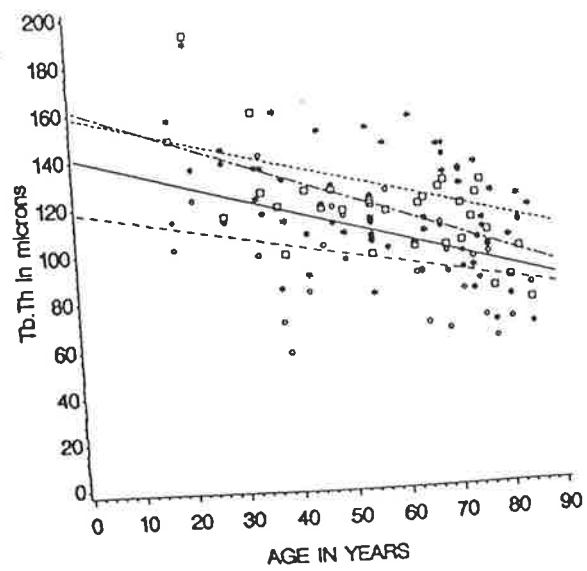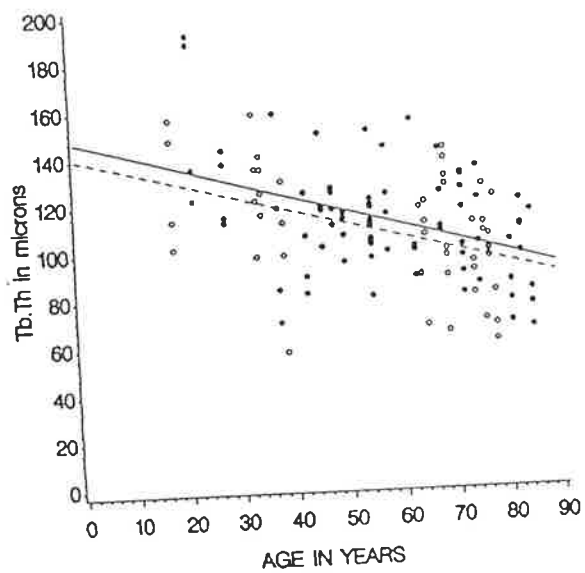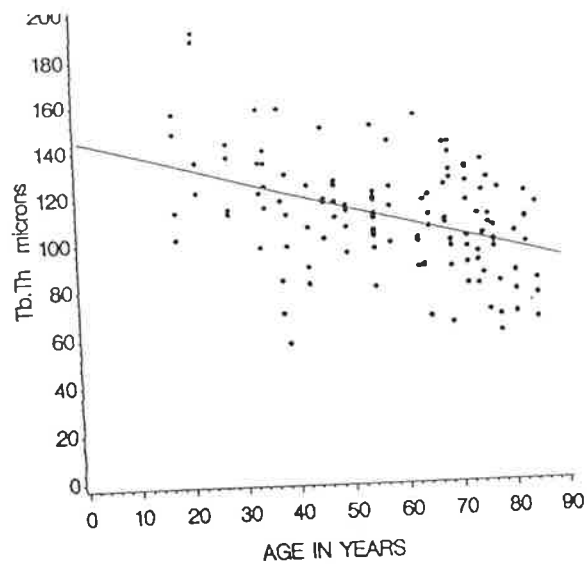
Table 5.7 : Values for trabecular spacing in the four regions examined in the main study group. n = 31 for each region.

Region	Mean $\pm$ S.D.
Medial Femur	266.73 $\pm$ 48.8
Medial Tibia	279.19 $\pm$ 72.7
Trochlea	251.19 $\pm$ 47.3
Patella	230.68 $\pm$ 46.7

Multiple t-tests : Trabecular spacing is signifcantly smaller in the patella than either the medial femur (p < 0.005) or medial tibia (p < 0.003).

Figure 5.26 : Graph of trabecular spacing in the femur versus trabecular spacing in the tibia.

r = 0.6177, p < 0.001, n = 31

Tb.Sp Tibia = 39.78 + 0.90 Tb.Sp Femur
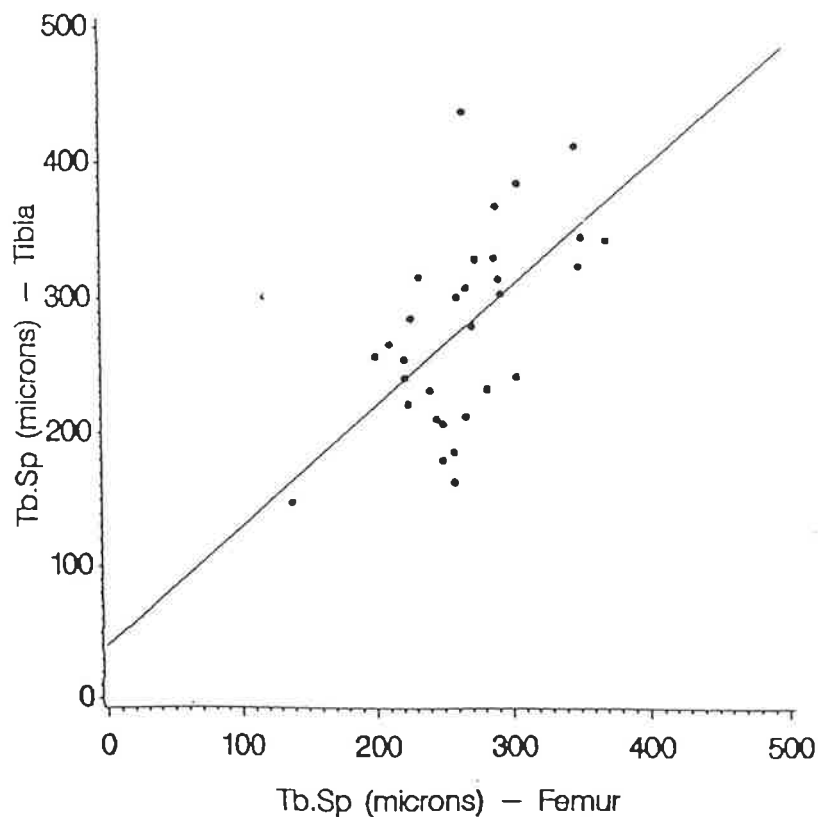
A significant positive correlation existed between Tb.Sp in the medial tibial plateau and that in the medial femoral condyle (Figure 5.26), but this was not the case in the patella and trochlea ($r = 0.2340$, $p > 0.20$, $n = 31$).

5.5 Cartilage Thickness

There was a negative correlation between BS/TV and cartilage thickness as measured by the Quantimet from the decalcified sections, but this was significant only in males (Figure 5.27).

There was no significant correlation between cartilage thickness and Tb.Sp in the main study group, but the correlations in the male and female subgroups were each significant, although disparate (Figure 5.28). Regionally there was also a significant positive correlation between Tb.Sp and cartilage thickness only in the medial tibia (Figure 5.29).

5.6 Calcified Cartilage

A positive correlation between BV/TV of the trabecular network and calcified cartilage thickness was significant in males only (Figure 5.30), and, regionally, it was significant only in the patella (Figure 5.31).

A positive correlation between Tb.Th and calcified cartilage thickness was significant only in males and only in the patella (Figures 5.32 and 5.33).

5.7 Subchondral Plate

A positive correlation was found between the BV/TV of the cancellous bone measured from the araldite sections and the BV/TV of the subchondral plate measured from the adjacent decalcified sections. This correlation was significant in the main study group (Figure 5.34), in both males and females (Figure 5.35), and regionally in the medial femoral condyle and medial tibial plateau, but not elsewhere (Figure 5.36).

Figure 5.27 : Graph of BS/TV versus cartilage thickness in the males.

Males :   r = - 0.3123, p < 0.01, n = 76

   Cartilage Thickness = 4648.97 - 327.7 BS/TV

Females : r = 0.2857, n = 48, Not significant

   Cartilage Thickness = 464.83 + 346.8 BS/TV

Figure 5.28 : Graph of trabecular spacing versus cartilage thickness by gender.

● —   Males : r = 0.3293, p < 0.01, n = 76

   Cartilage Thickness = 1219.56 + 6025.3 Tb.Sp

○ — — -   Females : r = - 0.3797, p < 0.05, n = 48

   Cartilage Thickness = 4246.71 - 7102.7 Tb.Sp

Figure 5.29 : Graph of trabecular spacing versus cartilage thickness by region.

Medial Femur : r = 0.1070, n = 31 Not significant

   Cartilage Thickness = 1741.27 + 1631.8 Tb.Sp

□ —·—   Medial Tibia : r = 0.4913, p < 0.01, n = 31

   Cartilage Thickness = 834.99 + 5935.4 Tb.Sp

Trochlea : r = 0.2426, n = 31. Not significant

   Cartilage Thickness = 1623.37 + 5672.6 Tb.Sp

Patella : r = 0.1617, n = 31. Not significant

   Cartilage Thickness = 1865.86 + 4422.2 Tb.Sp
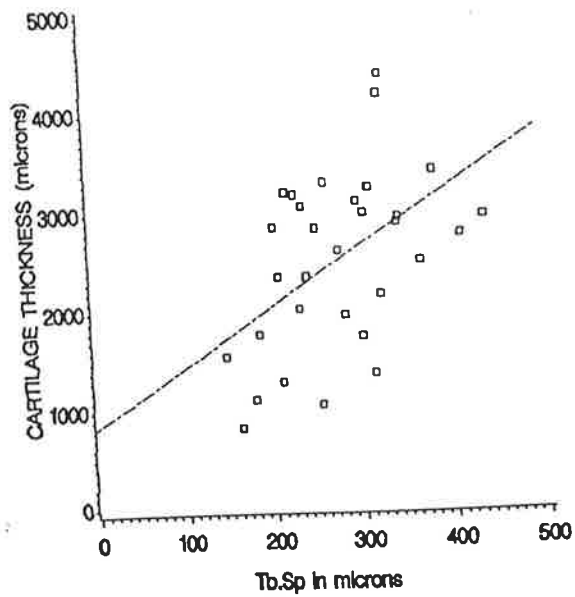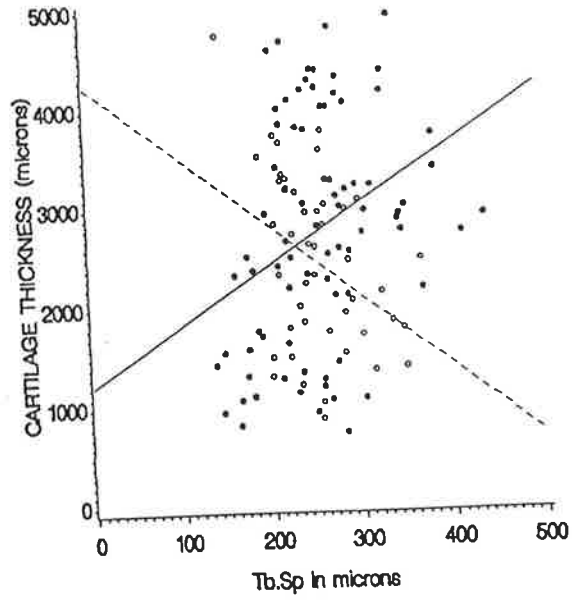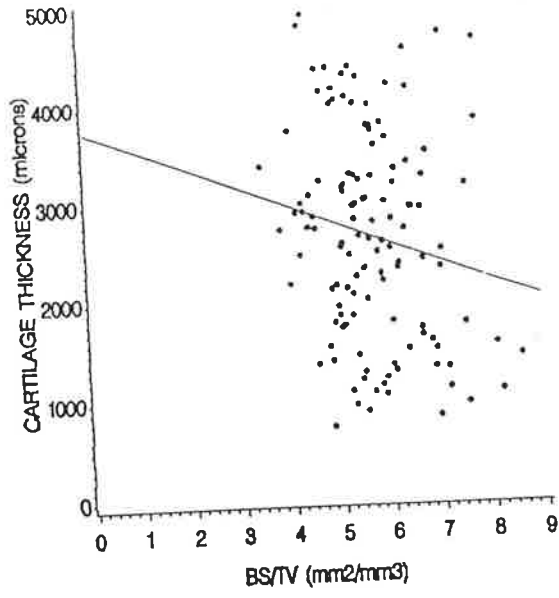
Figure 5.30 : Graph of BV/TV versus calcified cartilage thickness by gender.

Males : $r = 0.2784$, $p < 0.05$, $n = 76$

Calcified Cartilage = 80.37 + 1.8 BV/TV

Females : $r = 0.2857$, $n = 48$, Not significant

Calcified Cartilage = 150.00 + 0.64 BV/TV

Figure 5.31 : Graph of BV/TV versus calcified cartilage thickness by region.

Medial Femur : $r = -0.0359$, $n = 31$. Not significant

Calcified Cartilage = 144.12 - 0.32 BV/TV

Medial Tibia : $r = 0.2532$, $n = 31$. Not significant

Calcified Cartilage = 94.66 + 1.66 BV/TV

Trochlea : $r = 0.03418$, $n = 31$. Not significant

Calcified Cartilage = 152.57 + 0.35 BV/TV

*---- Patella : $r = 0.4833$, $p < 0.01$, $n = 31$

Calcified Cartilage = 15.29 + 3.8 BV/TV
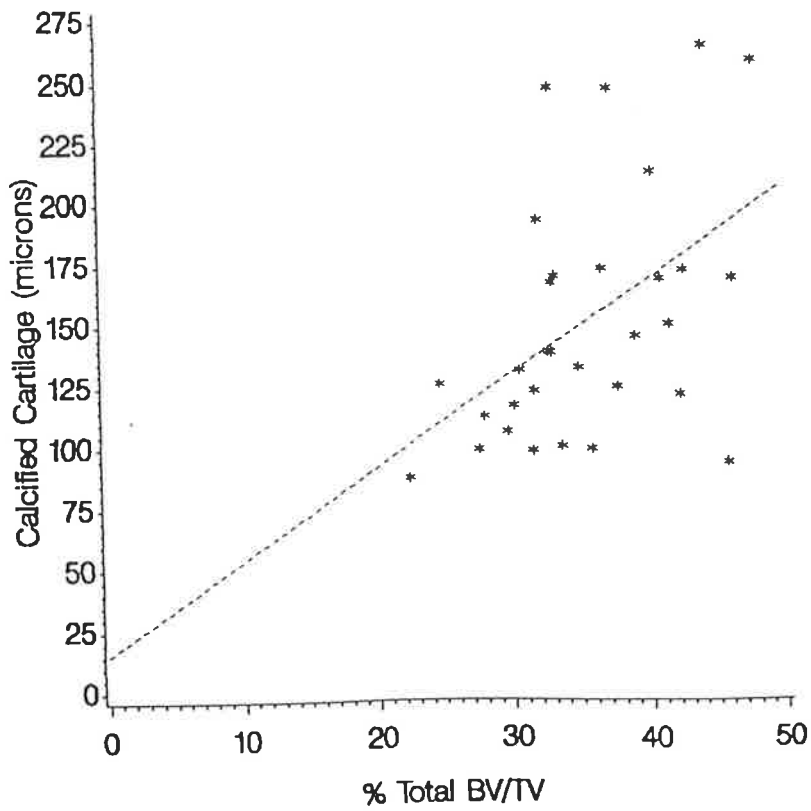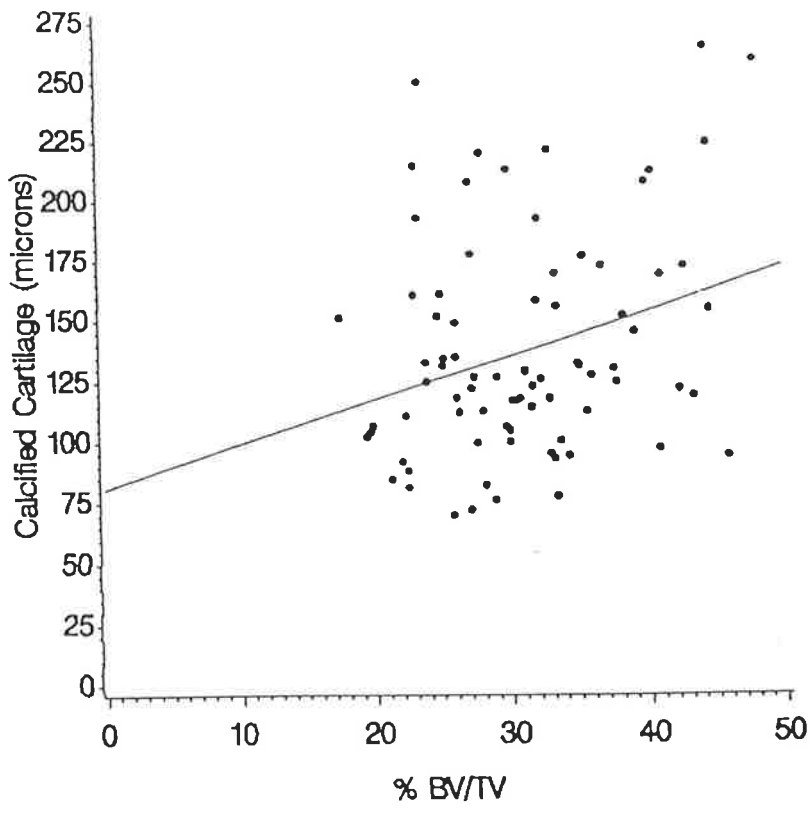
Figure 5.32 : Graph of trabecular thickness versus calcified cartilage thickness by gender.

Males : $r = 0.2370$, $p < 0.05$, $n = 76$

Calcified Cartilage $= 88.08 + 0.44$ Tb.Th

Females : $r = 0.1051$, $n = 48$. Not significant

Calcified Cartilage $= 141.98 + 0.25$ Tb.Th

Figure 5.33 : Graph of trabecular thickness versus calcified cartilage thickness by region.

Medial Femur : $r = 0.0416$, $n = 31$. Not significant

Calcified Cartilage $= 125.03 + 0.10$ Tb.Th

Medial Tibia : $r = 0.1796$, $n = 31$. Not significant

Calcified Cartilage $= 102.27 + 0.38$ Tb.Th

Trochlea : $r = 0.1796$, $n = 31$. Not significant

Calcified Cartilage $= 127.41 + 0.37$ Tb.Th

Patella : $r = 0.4432$, $p < 0.05$, $n = 31$

Calcified Cartilage $= 37.96 + 0.91$ Tb.Th
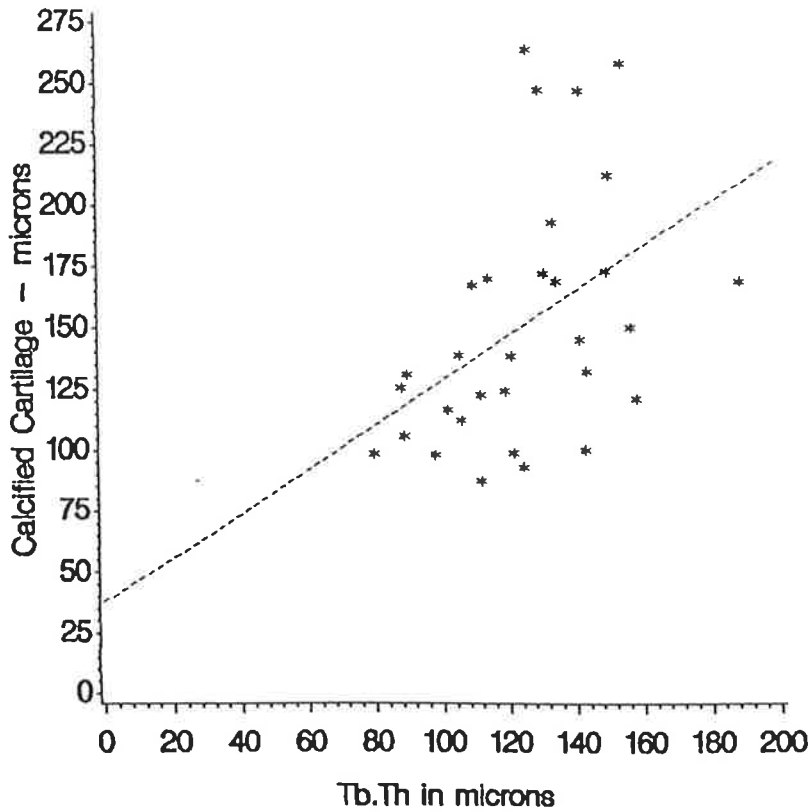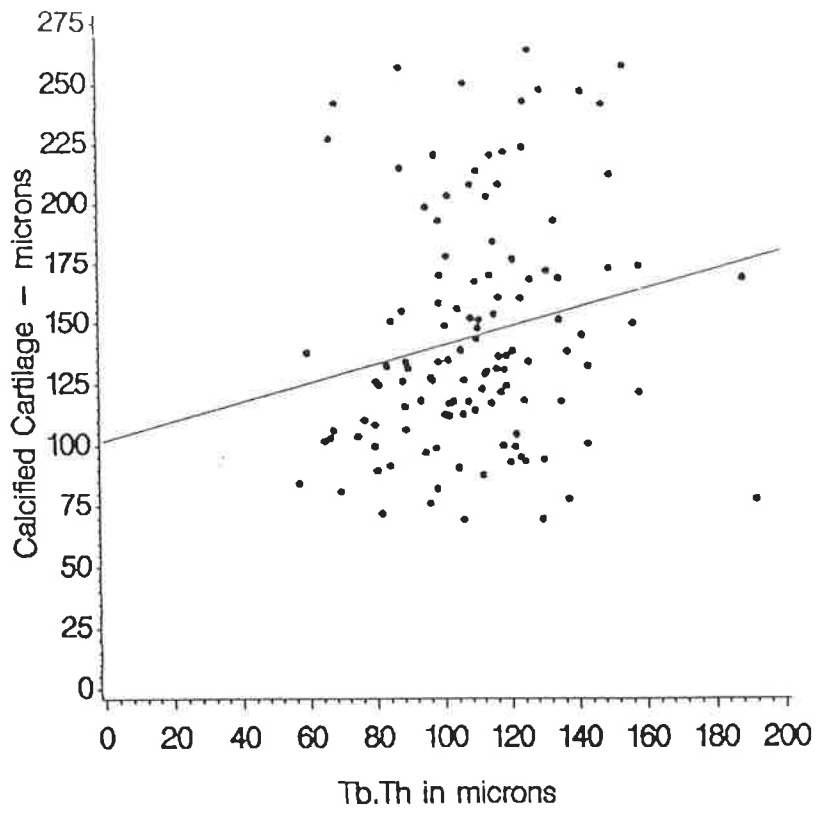
Figure 5.34 : Graph of cancellous BV/TV versus subchondral BV/TV in the main study group.

$r = 0.3720, p < 0.0001, n = 124$

Subchondral Plate BV/TV = 37.94 + 0.7 Cancellous BV/TV

Figure 5.35 : Graph of cancellous BV/TV versus subchondral BV/TV by gender

● ▬▬ Males : $r = 0.2479, p < 0.05, n = 76$

Subchondral Plate BV/TV = 46.17 + 0.5 Cancellous BV/TV

○ ▬ ▬ ▬ Females = $r = 0.5766, p < 0.0001, n = 48$

Subchondral Plate BV/TV = 22.44 + 1.3 Cancellous BV/TV

Figure 5.36 : Graph of cancellous BV/TV versus subchondral BV/TV by region

● ▬▬ Medial Femur : $r = 0.6712, p < 0.0001, n = 31$

Subchondral Plate BV/TV = 0.47 + 1.7 Cancellous BV/TV

□ ▬ · ▬ Medial Tibia : $r = 0.4050, p < 0.05, n = 31$

Subchondral Plate BV/TV = 52.5 + 0.6 Cancellous BV/TV

Trochlea : $r = -0.0472, n = 31$. Not significant

Subchondral Plate BV/TV = 60.3 - 0.1 Cancellous BV/TV

Patella : $r = 0.3287, n = 31$. Not significant

Subchondral Plate BV/TV = 50.5 + 0.4 Cancellous BV/TV
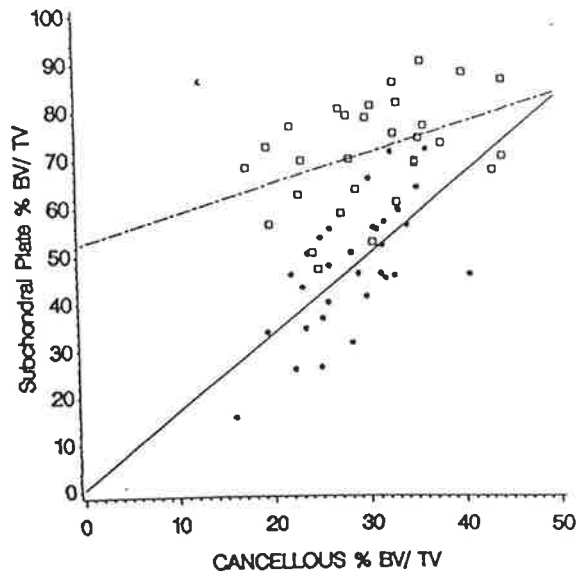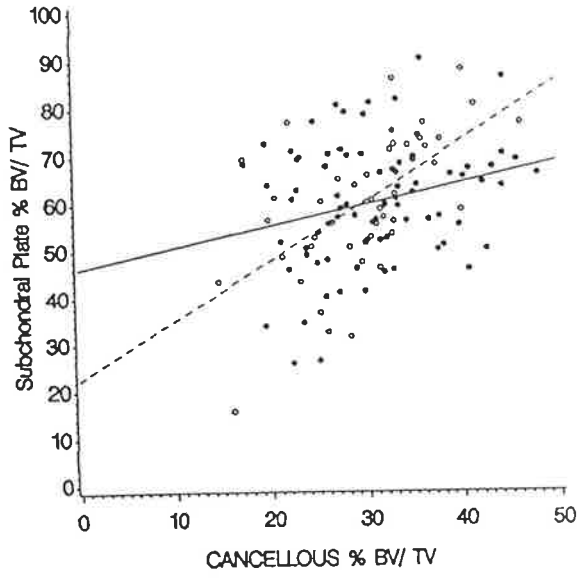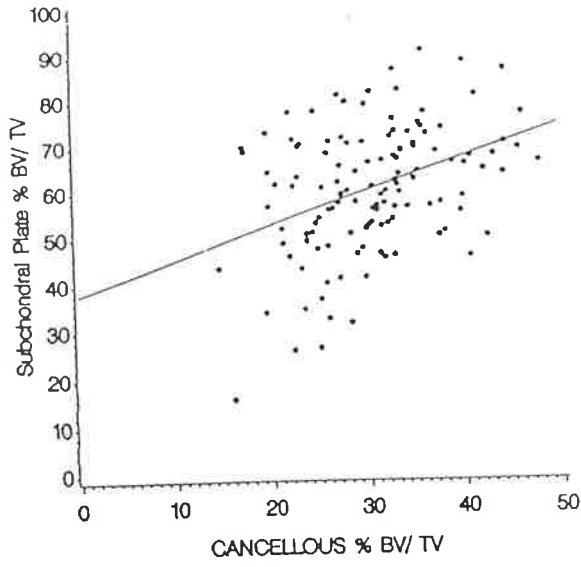
A significant positive correlation was also found between Tb.Th and the subchondral plate BV/TV in the main study group and both sexes (Figure 5.37 and 5.38). Regionally, however, the correlation was significant only in the medial femoral condyle and medial tibial plateau (Figure 5.39).

Figure 5.37 : Graph of trabecular thickness versus subchondral plate BV/TV in the main study group.

$r = 0.3976$, $p < 0.0001$, $n = 124$

Subchondral Plate BV/TV $= 36.07 + 0.22$ Tb.Th

Figure 5.38 : Graph of trabecular thickness versus subchondral plate BV/TV by gender.

Males : $r = 0.2226$, $p < 0.05$, $n = 76$

Subchondral Plate BV/TV $= 47.34 + 0.12$ Tb.Th

Females : $r = 0.6753$, $p < 0.0001$, $n = 48$

Subchondral Plate BV/TV $= 16.09 + 0.41$ Tb.Th

Figure 5.39 : Graph of trabecular thickness versus subchondral plate BV/TV by region.

Medial Femur : $r = 0.6299$, $p < 0.0001$, $n = 31$

Subchondral Plate BV/TV $= 4.78 + 0.41$ Tb.Th

Medial Tibia : $r = 0.3687$, $p < 0.05$, $n = 31$

Subchondral Plate BV/TV $= 50.76 + 0.18$ Tb.Th

Trochlea : $r = 0.1089$, $n = 31$. Not significant

Subchondral Plate BV/TV $= 53.07 + 0.05$ Tb.Th

Patella : $r = 0.2530$, $n = 31$. Not significant

Subchondral Plate BV/TV $= 54.55 + 0.08$ Tb.Th
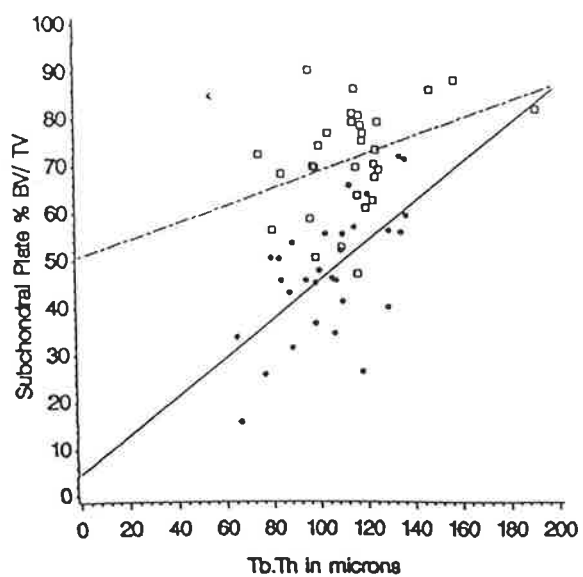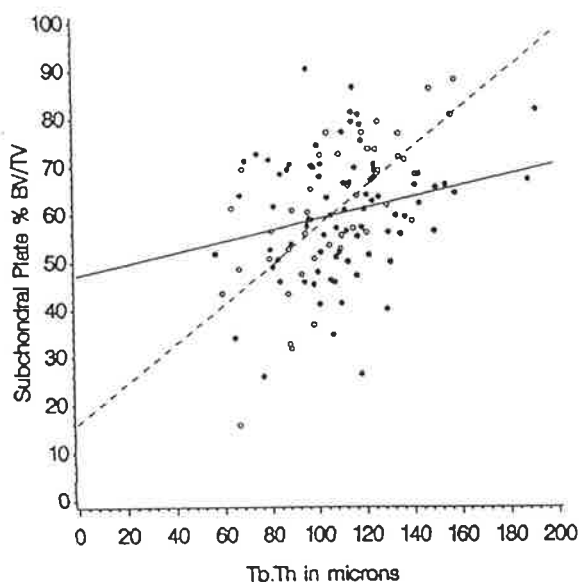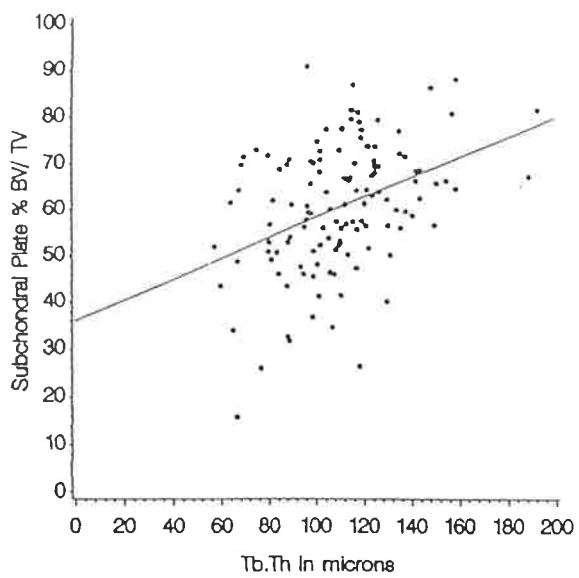
DISCUSSION

Although the examination of the structures at the bone-cartilage interface would suggest that activity in this region most influences the development of age-related cartilage damage, it may be such changes are secondary and that other factors may initiate cartilage damage. A possible mechanism by which the nature of the underlying cancellous bone may influence cartilage condition has been put forward by Radin et al [111,112], and thus the examination of the structure of the cancellous bone within the medial tibia and femoral condyle, the trochlea and the patella was performed using the Quantimet image analysis system.

Bone loss with increasing age is a well known phenomenon in the head of the femur [34], the iliac crest [10,92,103,141] and the lumbar vertebrae [30]. The current study has shown that there is also a significant decrease in BV/TV in the knee with increasing age in both males and females, a decrease which is significant in all of the regions examined apart from the patella (Figure 5.5). In the three regions where the correlation was significant, the medial tibia, the medial femur and the trochlea, there was no difference between the slopes of the regression lines, nor in the intercepts. Thus, the nett loss of mineralised bone from the trochlea, femur and tibia is similar, and is unaffected by regional differences in loading. It can be determined from the correlation coefficient that only 9% of the variance in BV/TV within the main study group can be accounted for by age (Figure 5.3). In the female subgroup, this figure rose to nearly 20% (Figure 5.4), reflecting the more profound influence of age on mineralised bone loss in females, presumably as a result of the effect of the menopause on bone volume.

Age-related bone loss is generally accepted to be the result of loss of entire trabeculae from the cancellous network [1,10,103]. This is reflected by an increase in Tb.Sp, as changes in Tb.Th alone are rarely sufficient to be reflected by changes in the Tb.Sp [34]. In contrast to the femoral head [34] and iliac crest [1,103], there

was no significant change in Tb.Sp in the knee with increasing age. Bone loss in the knee, therefore, is not the result of trabecular loss, but, as can be seen in the correlation between age and Tb.Th (Figure 5.23), the result of trabecular thinning alone. This decrease in Tb.Th with increasing age was seen in all regions of the knee, including the patella, which, however, showed no significant decrease in BV/TV with age. This finding may be the result of the fact that the patella has a significantly higher initial BV/TV , and although there is a significant thinning of trabeculae with increasing age, it is not sufficient to affect BV/TV. There were no significant differences in either intercepts or slopes of the regression lines in the four regions (Figure 5.25), indicating a constant degree of trabecular thinning throughout the knee. The rate at which Tb.Th changes with age was not significantly different in females and males ($p > 0.05$), but, despite this, there was a significant difference in the loss of mineralised bone with age between the sexes. For the same fall in BV/TV, females will show a greater decrease in Tb.Th than males, and this may be a consequence of the effect of the menopause on bone structure in women. In contrast to published work on the different regions within the femoral head [34], there were no significant regional differences in the rate of change in Tb.Th associated with changes in BV/TV.

As BV/TV decreases, there is a non-linear increase in Tb.Sp (Figure 5.12). This was more rapid in males than in females, and more rapid in the medial tibia and patella compared to the other regions (Figures 5.13, 5.14). In this study population, BV/TV rarely falls below 20%, the point at which Tb.Sp begins to increase rapidly, and thus this relationship rarely becomes significant in age-related bone loss in the knee. The non-linear relationship between BV/TV and Tb.Sp seen here, has been previously described by Snyder et al in the proximal femur and within the lumbar vertebrae [129,130] : that this relationship is seen also in the knee suggests that it represents a universal phenomenon.

Continued intermittent loading is a potent stimulator of bone formation [20], which undoubtedly influences bone loss in the knee. Thus, in areas where bone

formation is stimulated by local mechanical factors, there is a strong incentive to conserve an intact trabecular network, therefore no trabeculae are lost with increasing age. There is some support for this hypothesis in a study of the femoral head [34] where the loss of trabeculae, reflected by an increase in Tb.Sp, occurred far earlier in the less stressed principal tensile region when compared to the weight bearing principal compressive region. All areas examined in the current study can be considered to have been taken from the equivalent 'principal compressive' regions of the patellofemoral and tibiofemoral joints. This explains the absence of any significant difference in BV/TV between the sexes, since, in the principal compressive region of the femoral head, no such difference in BV/TV between males and females existed [34].

BS/TV showed no variation with age, in contrast to the iliac crest [92] and the femoral head [34] where a significant decrease with age was seen. In one study of the iliac crest there was a decrease in BS/TV only after the age of 60 [72]. This discrepancy in the effect of age on BS/TV within the knee may be related to the fact that no trabeculae appear to be completely resorbed during age-related bone loss in the knee. Comparison of the correlation coefficients reveals that the percentage of variance in BS/TV accounted for by BV/TV is greater in the medial tibia (52%) than in the medial femur (16%) (Figure 5.8). A similar situation was seen in the femoral head where a greater percent of the variance in BS/TV was accounted for by BV/TV in the principal tensile region than in the principal compressive region. Thus decreases in BV/TV have less influence on BS/TV in the medial femur than in the medial tibia.

The observation that the BV/TV of the subchondral bone plate correlated strongly with both BV/TV of the trabecular network and Tb.Th (Figures 5.34,5.37), is similar to the result obtained by Noble and Alexander [99] in the tibial plateau. The correlations in the present study were significant only in the tibial plateau and the femoral condyle. Thus, the hypothesis of strong pillars being necessary to uphold a thicker subchondral plate [99] appears to be valid only for

areas directly involved in weight bearing, unlike the patella and trochlea. The thinning of the subchondral plate as BV/TV decreases is more rapid in males than in females (Figure 5.35, $p < 0.01$); and, whilst cancellous BV/TV accounts for only 6% of the variance in subchondral plate BV/TV in males, the figure rises to 33% in females. This suggests that bone loss in females occurs more uniformly throughout both the subchondral plate and the cancellous network than in males, in whom bone loss with increasing age would appear to be predominantly from the trabecular network. Thus women are more susceptible to fracture as a result of age-related bone loss, since bone will be lost from both cortical bone and the cancellous bone network. The rate of subchondral plate thinning as BV/TV decreases is significantly more rapid in the medial femur than the medial tibia (Figure 5.36, $p < 0.02$), and the percentage of variance in subchondral plate BV/TV accounted for by total BV/TV is greater in the medial femur than in the medial tibia. Therefore, it would appear that bone loss from the medial femur is more evenly distributed across the subchondral plate and the cancellous bone than in the medial tibia. The marked density of the tibial subchondral plate due to its mechanically weak concave structure has been discussed earlier, and the slower decline in density as BV/TV decreases, indicates that other influences, presumably mechanical, affect the density of the subchondral plate. As BV/TV decreases in the medial tibia with age, the loss of mineralised bone appears mainly from the cancellous bone, and not from the subchondral plate where mineralised bone remains in an effort to maintain the mechanical integrity of the weak concave structure of the tibial facet [127].

The correlation of both BV/TV and Tb.Th with calcified cartilage thickness was significant in males and in the patella alone (Figures 5.30 to 5.33). The role of calcified cartilage is thought to be in providing either a zone of transitional stiffness or a strong connection of bone to cartilage. As BV/TV increases and the trabecular network becomes stiffer [151], there may be a greater requirement for an area of intermediate stiffness as provided by calcified cartilage. Alternatively, the two factors may be related to a third factor such as body size and weight : larger

individuals may have more bone, thicker trabeculae and more calcified cartilage. It is interesting, however, that the correlation is significant only in the patella, suggesting that the interaction of bone and calcified cartilage is not important in direct weight bearing regions, such as the tibia and femur, but rather where shear forces predominate, areas where calcified cartilage has a role in converting shear into compressive forces.

The relationship between Tb.Sp and total cartilage thickness is unusual: although no significant relationship exists in the main study group, a significant inverse relationship exists in males and a direct relationship exists in females (Figure 5.28). This result may well be spurious, since there is no obvious reason why the two sexes would exhibit such a different pattern. Cartilage thickness was shown earlier to be an indicator of cartilage degeneration, and areas of high bone density are associated with degeneration. The fact that despite a significant correlation between Tb.Sp and cartilage thickness, no correlation exists between cartilage thickness and BV/TV indicates that it is not the amount of bone, but how it is arranged, that most influences cartilage condition.

One of the most striking features of this study is the marked difference in the bone histomorphometric parameters of the patella compared to the other regions examined. Blocks taken from the patella have a significantly greater BV/TV, thicker trabeculae and smaller trabecular spacing. In not displaying a significant negative correlation between BV/TV and age, the patella differs from all other regions examined. The patella is also the only region where there is a significant correlation between both BV/TV and trabecular thickness, and calcified cartilage thickness. These correlations may be because BV/TV, subchondral plate thickness and calcified cartilage all being related to a third factor such as age, but it has already been shown that calcified cartilage thickness is unrelated to age (Chapter 4). This third factor could be body size or functional demand, but then a correlation with total cartilage thickness would also be expected. Alternatively, calcified cartilage,

the cancellous bone network and the subchondral plate may be exhibit these correlations because they are components of a single functional unit, ensuring the optimum compliance and close adherence of bone and cartilage in an area of high shear forces.

The unique characteristics of the patella also contribute to the difference between the patellofemoral and tibiofemoral joints. Whereas the tibia and femur do not differ significantly from each other in terms of BV/TV, BS/TV, Tb.Th or Tb.Sp, the patella and trochlea exhibit significant differences in BV/TV and Tb.Th, and the only significant correlation between the two is in BV/TV. The structure of bone is the result of the functional demands made upon it, and the similarity in structure of the tibia and femur is not surprising since they are both involved in weight-bearing. The patella and trochlea, however, have different functional demands made upon them even though they articulate with one another: the trochlea is part of the axial, weight bearing, skeleton, whereas, the patella is not directly involved in weight bearing and articulates not only with the trochlea but also with the femoral condyle. The patellofemoral joint is subject to compressive forces of smaller magnitude than those in the tibiofemoral joint, but over similar contact areas [62,100]. Despite this, the cancellous bone in the patella is far denser than elsewhere. This may be a result of the considerable tensile forces to which the patella is exposed, tethered to the tibia at one end, and pulled at the other by one of the largest muscles in the body. The denser, thus stiffer bone [151], since it is less able to absorb potentially damaging forces, may contribute to the high degree of cartilage damage seen in the patella, and this may be aggravated by the shear forces to which the patella is exposed as it articulates with both the trochlea and femoral condyle.

CONCLUSIONS

1. Bone loss in the knee is not the result of loss of structural elements, as it is in other regions of the skeleton, but rather as the result of the thinning of existing trabeculae. High loading may encourage retention of an intact trabecular network within the knee.

2. Age related bone loss has a significantly different pattern in males, where it is predominantly from the trabecular network, compared to females where bone loss occurs more evenly from both the subchondral plate and trabecular network.

3. The thickness of the subchondral plate is directly related to BV/TV and Tb.Th in those areas primarily involved in weight bearing, namely the medial femur and medial tibia.

4. A significant correlation between BV/TV, Tb.Th and calcified cartilage thickness exists in the patella, where shear forces predominate, but not in regions more directly involved in weight bearing.

5. The fact that cartilage thickness is related to Tb.Sp and not to BV/TV indicates that it is the arrangement of bone, rather than bone volume alone that influences cartilage thickness.

6. The cancellous bone in the patella is significantly different compared to bone from the other regions, having a greater BV/TV, thicker trabeculae and a smaller trabecular spacing. It also does not show the significant decrease in BV/TV with age seen elsewhere in the knee. Parameters from the two sides of the tibiofemoral joint are very similar, whereas the patella and trochlea are very different. These factors may explain the propensity for early and severe cartilage damage in the patella,

where a dense bone network, absorbing a smaller proportion of impulse loading forces is present throughout life.

CHAPTER 6 : MACROSCOPIC MAPPING OF FOCAL CONTACTS

For some time articular cartilage in the skeletally mature individual has been considered to be a completely avascular structure, but work by Holmdahl and Ingelmark and others [55,59,69,153] has shown blood vessels extending from the marrow space to the deeper layers of cartilage. The role of these 'focal contacts' has been the subject of some debate, with two main schools of thought predominating : (1) that focal contacts provide nutrition to the deeper layers of cartilage; and, (2) that focal contacts are involved in the formation and remodelling of the subchondral plate. In either case, a possible role for focal contacts in the development of cartilage changes can be proposed: if they are involved in cartilage nutrition, any fall in their numbers will result in cartilage degeneration because of inadequate nutrition. Alternatively, if focal contacts are involved in remodelling of the subchondral plate, an increase in bone formation will result in a decrease in bone compliance and the cartilage will then be exposed to damaging forces from which it was previously shielded [111,112]

In Chapter 4, histological examination of the bone-cartilage interface failed to reveal any relationship between focal contact numbers and either cartilage condition or thickness. This may have been because the sections examined were not representative of the articular surface as a whole. Thus, in an attempt to explain the different patterns of cartilage damage within the regions of the knee, and any possible relationship between cartilage condition and focal contact numbers, the vascularity of the subchondral plate throughout the medial femur, medial tibia, trochlea and patella was studied in 17 males and 14 females, ranging in age from 18 to 90 years.

Each region was mapped and then divided using a grid of one centimetre squares and focal contacts were counted within each square as described in Chapter 2. Focal contacts numbers were expressed in terms of the number per square millimetre, the area of each region being obtained from digitisation of

the contact maps. In order to examine any possible link between cartilage condition and focal contact numbers, values from intact one centimetre squares only were used. In each square, the condition of the overlying cartilage was assessed as intact cartilage, slight fibrillation, moderate fibrillation and advanced changes which included severe fibrillation, fibrocartilage and bone exposure.

RESULTS

6.1 Focal contacts / millimetre^2

The mean age of males was 56.99 ± 17.6 and that of females 62.53 ± 21.6, which was significantly different on paired t-testing ($p < 0.0001$). The mean number of focal contacts / mm^2 was 0.7081 ± 0.62. There were no significant differences between right and left knees ($p > 0.50$), but the value was significantly higher in males than in females on Wilcoxon rank testing ($p < 0.005$, Table 6.1). There were no significant regional differences (Table 6.2).

A significant negative correlation was found between age and the number of focal contacts / mm^2 (Figure 6.1). This was significant in males but not females (Figure 6.2), and in the medial femur and patella but not elsewhere (Figure 6.3).

6.2 Focal contacts / whole grid square

The mean number of focal contacts in whole grid squares was found to be 97.33 ± 111.4, and again was significantly higher in males than in females on Wilcoxon rank testing (Table 6.3). Regionally the values were not significantly higher in any one region (Table 6.4).

Multiple Wilcoxon rank tests revealed that the number of focal contacts was significantly higher in squares with intact cartilage than in squares with any form of cartilage change (Table 6.5).

Table 6.1 : The number of focal contacts / mm2 in males and females in the main study group.

	MIN	25%ile	MEDIAN	75%ile	MAX
MALES	0.0717	0.3024	0.4252	0.6950	1.970
FEMALES	0.0728	0.1695	0.2761	0.5115	0.8977

$p < 0.005$ on Wilcoxon rank testing

Table 6.2 : Number of focal contacts / mm2 in the four regions examined.

	MIN	25%ile	MEDIAN	75%ile	MAX
MF	0.0297	0.2424	0.4072	0.7749	2.5935
TR	0.0054	0.2286	0.6801	0.9262	3.2088
MT	0.0178	0.2466	0.5604	1.0672	2.4701
PA	0.1266	0.3348	0.6971	1.0759	3.5449

Multiple Wilcoxon rank tests : No significant regional differences

Figure 6.1 : Graph of age versus the number of focal contacts per mm2 in the total study group.

$$r = -0.3608, p < 0.0001, n = 124$$

$$\text{Focal Contacts/mm}^2 = 24.1 \, \text{Age}^{-0.9}$$

Figure 6.2 : Graph of age versus the number of focal contacts per mm2 by gender.

● ——

Males : $r = -0.3526, p < 0.0001, n = 68$

$$\text{Focal contacts/mm}^2 = 63.43 \, \text{Age}^{-1.1}$$

Females : $r = -0.2493, n = 56$, Not significant

$$\text{Focal contacts/mm}^2 = 13.89 \, \text{Age}^{-0.83}$$

Figure 6.3 : Graph of age versus the number of focal contacts per mm2 by region.

● ——

Medial Femur : $r = -0.5956, p < 0.001, n = 31$

$$\text{Focal contacts/mm}^2 = 96.45 \, \text{Age}^{-1.28}$$

Medial Tibia : $r = -0.3406, n = 31$, Not Significant

$$\text{Focal contacts/mm}^2 = 17.89 \, \text{Age}^{-0.82}$$

Trochlea : $r = -0.1957, n = 31$, Not Significant

$$\text{Focal contacts/mm}^2 = 18.32 \, \text{Age}^{-0.83}$$

✳ ------

Patella : $r = -0.3595, p < 0.05, n = 31$

$$\text{Focal contacts/mm}^2 = 10.62 \, \text{Age}^{-0.65}$$
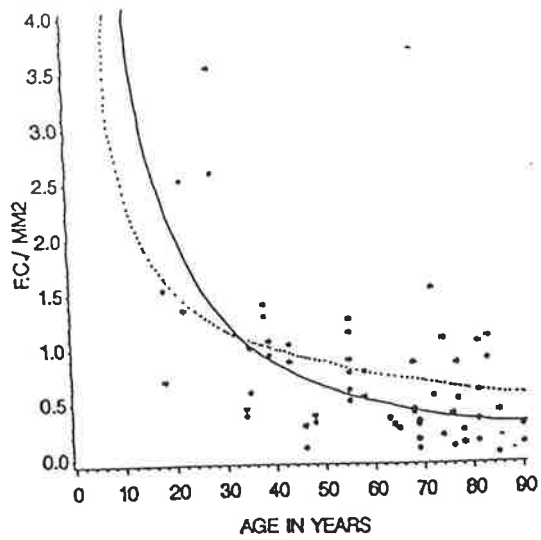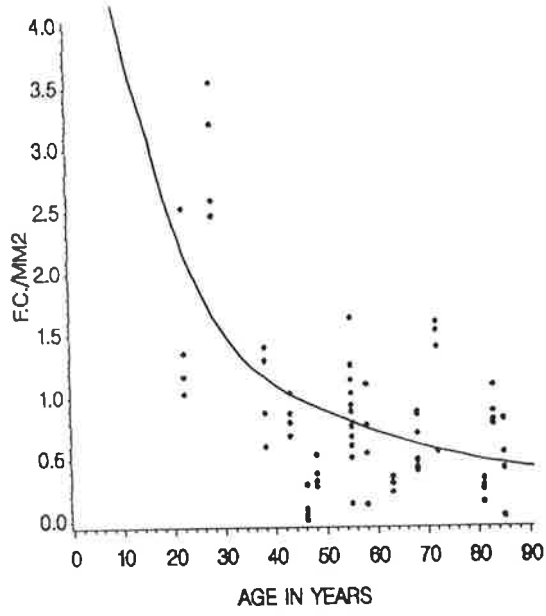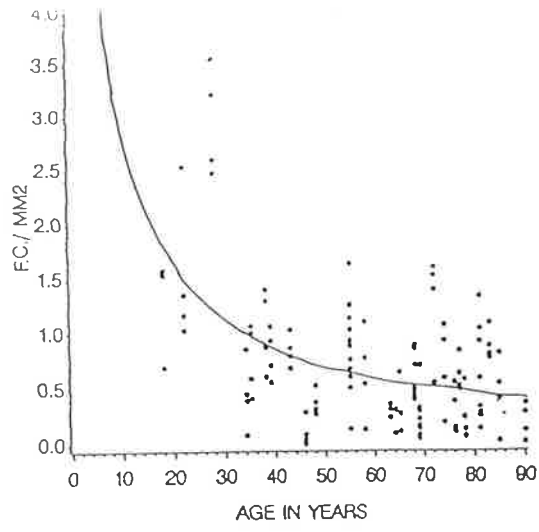
Table 6.3 : Number of focal contacts / whole grid square in males and females in the main study group.
Males n = 733; Females n = 392

	MIN	25%ile	MEDIAN	75%ile	MAX
MALES	0	28	74	149	944
FEMALES	0	13	42	93	501

Wilcoxon rank testing p < 0.0001

Table 6.4 : The number of focal contacts / intact grid square in the main study group by region.

	MIN	25%ile	MEDIAN	75%ile	MAX
MF n=422	0	13	42	100	944
MT n=206	0	19	63	122	451
TR n=323	0	25	71	151	708
PA n=174	0	47	105	172	696

No significant difference on Wilcoxon rank testing

Table 6.5 : The number of focal contacts / intact grid square by cartilage condition.

	MIN	25%ile	MEDIAN	75%ile	MAX
INTACT	0	20	76	169	944
SLIGHT	0	20	65	127	445
MODERATE	0	20	52	95	568
ADVANCED	0	23	68	124	377

Normal n = 399   Moderate n = 307
Slight n = 317   Advanced n = 110

Multiple Wilcoxon tests :
          Squares with intact cartilage have significantly more focal contacts than all otherr squares (p < 0.05).

DISCUSSION

The exact role of focal contacts is unclear, but the various forms of focal contact seen in the subchondral bone histologically suggest that they are involved in remodelling calcified cartilage and the subchondral bone plate, and recent work has confirmed the formation of bone around focal contacts within the subchondral bone in mice [8]. It is well known that bone responds to the functional demands made upon it, and there is no reason why the subchondral bone plate should be different from the rest of the skeleton. The interdigitation of the bone-cartilage interface has been proposed to play a major role in the ability of the joint to deal with shear forces and if this area is to respond appropriately to changes in such forces, then bone remodelling is to be expected. However, the possibility that focal contacts may have a role in the nutrition of the deeper layers of cartilage cannot be excluded.

The sex related difference in focal contact numbers may well be the result of the significant difference in the ages between the male and female groups.

The decrease in the number of focal contacts with age described by a number of previous authors [67,85,153] has been confirmed by the present study. Lane et al [67] found a slight but definite increase in focal contact numbers in the over 70 age group. The decrease in focal contact numbers is most rapid in early life. The high number of focal contacts seen in younger individuals is because of their role in the development and growth of the subchondral plate, and once skeletal maturity is achieved their numbers rapidly decrease with only a few focal contacts remaining to allow the subchondral plate and calcified cartilage to respond to changing functional demands, resulting in the low-grade continuous remodelling and growth in the long bones of adults as proposed Bullough [13].

Focal contact numbers have previously been found to be greater in areas of relatively high load [67,153] and in areas with thick cartilage [153]. In the present study, neither the number of focal contacts / mm^2 or of focal contacts per grid square showed any regional variation. This difference may well be the result of the inclusion of areas of both high and low loading into the calculations. The failure of regional focal contact density to reflect the significant differences in cartilage thickness seen in Chapter 4, argues against focal contacts being involved in cartilage nutrition, since the thicker cartilage of the trochlea does not show any increase in vascularity.

Grid squares with intact cartilage had significantly more focal contacts than did squares with any form of cartilage damage (Table 6.5). There are a number of possible explanations for this association between cartilage condition and vascularity. Firstly, cartilage condition is known to deteriorate with age (Chapter 3), and focal contact numbers have also been shown to decrease with age, therefore those grid squares with advanced cartilage changes are more likely to be from older specimens, which will have fewer focal contacts. Secondly, the decrease in focal contacts with age may cause cartilage degeneration, with impaired nutrition resulting in cartilage being unable to maintain its integrity in the face of normal functional demands. Alternatively, if cartilage damage results from decreased bone compliance as a result of a thick subchondral plate, the visibility of the focal contact from above may be obscured and cartilage damage is due to the thickened plate rather than from any change in vascularity. This is unlikely to be the case, however, since an absolute fall in focal contacts has been shown in the articular surfaces examined.

Grid squares showing the very earliest forms of cartilage change already show a significant decrease in focal contact numbers, but there is no significant change in focal contact numbers between slight and advanced forms of damage. This difference in the focal contact numbers may simply be a result of the

probable age difference between the specimens from which intact and degenerated grid squares originated. Alternatively if focal contacts do have a significant role in the development of age-related cartilage changes, it can only be as an initiating factor: the progression of cartilage damage is not affected by changes in subchondral vascularity.

The results of the macroscopic mapping argue against focal contacts being involved in the nutrition of cartilage, since regions with thicker cartilage do not have significantly more focal contacts, and although their role in remodelling the subchondral bone plate and calcified cartilage cannot be proven in this morphologic study, the results do not exclude this possibility which may be more relevant in other sites within the skeleton.

CONCLUSIONS

1. A significant non-linear correlation between age and focal contact numbers has been demonstrated, with a rapid decrease in focal contact numbers in early adult life.

2. The regional differences in cartilage thickness seen in Chapter 4 are not associated with any significant regional variation in focal contact numbers.

3. Areas with intact cartilage have significantly more focal contacts than areas with any form of cartilage damage. There is no significant difference in focal contact numbers between the various forms of cartilage damage. The decrease in focal contact numbers appears an early feature, and the progression of cartilage damage is not the result of further changes in subchondral vascularity.

4. The possibility that focal contacts are involved in the remodelling of the bone-cartilage interface throughout life cannot be excluded.

CHAPTER 7 : TRABECULAR MICROFRACTURES

Subchondral cancellous bone is important in a joint's ability to absorb potentially damaging impulse forces [111,112]. It has been postulated that stiffening of subchondral bone may decrease the amount of energy that it is capable of absorbing, exposing the cartilage to destructive forces from which it is normally protected [111,112]. Increased bone stiffness may arise from an increase in the amount of mineralised bone [114,115], changes in the arrangement of trabeculae [105] or from the presence of healing trabecular microfractures [114]. In order to examine the possible role of trabecular microfracture in the development of age-related changes in the knee, single coronal slices from the medial femoral condyle and medial tibial plateau, and transaxial slices of the patella and trochlea, were taken for examination. Specimens from 15 individuals, 8 female and 7 male, ranging in age from 18 to 90 were examined.

RESULTS

Examination of the composite maps of each region (Figure 7.1) shows that there is a definite concentration of trabecular microfractures adjoining the lateral aspect of the medial tibial plateau, that is, in the area underlying the intercondyloid eminence of the tibia. In the medial femoral condyle the localisation of trabecular microfractures is less marked, although there is a tendency for them to be located in the medial aspect of the medial femoral condyle. In both the medial femoral condyle and medial tibial plateau, the trabeculae which display callus formation are equally likely to be oriented perpendicular or parallel to the articular surface. In the trochlea, there is a concentration of trabecular microfractures some distance from the articular surface, and more than half of the fractured trabeculae are oriented parallel to the articular surface. The three trabecular microfractures seen in the patella were restricted to that area furthest from the articular surface and all were in trabeculae parallel to the articular surface.
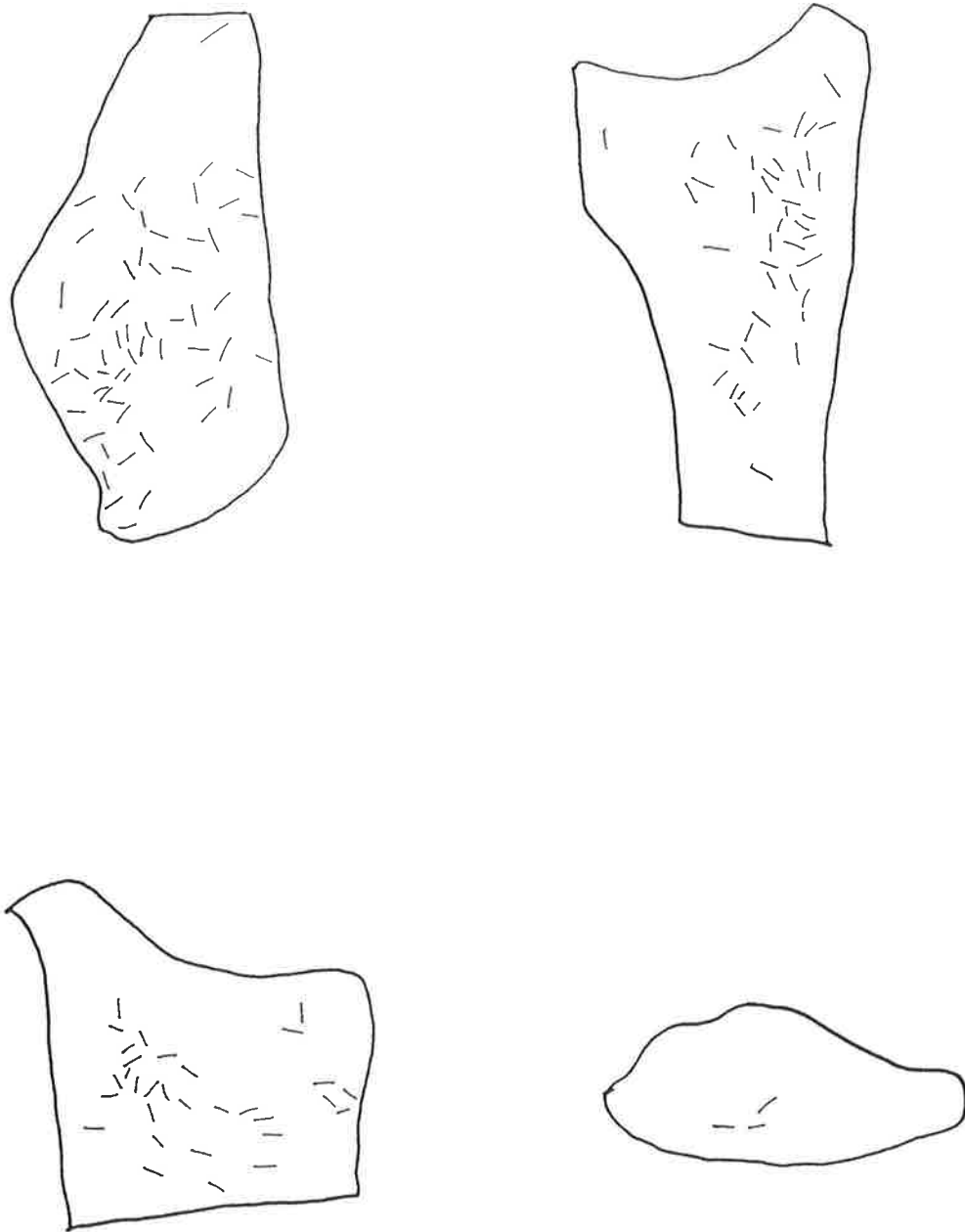
Figure 7.1 : Composite maps of the coronal slices of the medial femur and medial tibia, and the transaxial slices of the patella and trochlea, showing the distribution of healing trabecular microfractures form the 15 cases examined. Each stroke indicates the position of the fractured trabecula.

The mean number of trabecular microfractures in each case was 7.00 ± 8.2 and the only significant regional difference found was between both the medial femur and the trochlea, and the patella (Table 7.1). There was no significant male - female difference .

A significant non-linear positive correlation between age and the number of trabecular microfractures was seen for the total group (Figure 7.2). This age related increase was significant in females but not males (Figure 7.3), and was significant in all regions except the patella (Figure 7.4).

Histological data obtained from the opposite knee in each case was correlated with the trabecular microfracture data. There was a significant negative correlation between the number of trabecular microfractures and the trabecular thickness in the total study group (Figure 7.5), but not within individual regions. A significant negative correlation was also found between trabecular microfracture numbers and BV/TV (Figure 7.6), that was regionally significant in the trochlea alone (Figure 7.7).

There was no significant correlation between trabecular microfracture numbers and the condition of cartilage as assessed by the Mankin score from the decalcified sections from the opposite knee. A significant negative correlation was found between the number of trabecular microfractures and the thickness of cartilage measured from the decalcified sections using the Quantimet (Figure 7.8). Regionally this was significant in the medial femur and medial tibia (Figure 7.9).

No significant correlation was found between focal contacts and trabecular microfractures in the total study group nor in any region except the patella ($r = -0.5830$, $p = 0.0287$, $n = 15$).

A significant positive correlation was found between the numbers of trabecular microfractures within all regions, except the patella (Figure 7.10-7.12).

Table 7.1 : Number of healing trabecular microfractures in the four regions of the knee.

	MINIMUM	25%ile	MEDIAN	75%ile	MAXIMUM
MF	0	0	1	4	11
TR	0	0	1	4	9
MT	0	0	0	4	8
PA	0	0	0	0	1

Multiple Wilcoxon rank tests -
Significantly more trabecular microfractures are seen in the medial femur and the trochlea than in the patella ($p < 0.004$ in both cases).

Figure 7.2 : Graph of age versus the number of healing trabecular microfractures in the total study group.

$$r = 0.5652, p < 0.0001, n = 60$$

$$TMF = 0.12\,e^{0.04\ Age}$$

Figure 7.3 : Graph of age versus the number of healing trabecular microfractures (TMF) by gender.

Females : $r = 0.7717, p < 0.0001, n = 28$

O − − − $TMF = 0.37\,e^{0.03\ Age}$

Males : $r = 0.3001, n = 32$. Not significant

$$TMF = 7x10\text{-}4\,e^{0.10\ Age}$$

Figure 7.4 : Graph of age versus the number of healing trabecular microfractures (TMF) by region.

Medial Femur : $r = 0.6675, p < 0.01, n = 15$

● — $TMF = 0.13\,e^{0.05\ Age}$

Medial Tibia : $r = 0.7077, p < 0.01, n = 15$

□ − · − $TMF = 0.10\,e^{0.05\ Age}$

Trochlea : $r = 0.7202, p < 0.01, n = 15$

O − − $TMF = 0.24\,e^{0.04\ Age}$

Patella : $r = 0.3471, n = 15$ Not significant

$$TMF = 5x10\text{-}5\,e^{0.10\ Age}$$
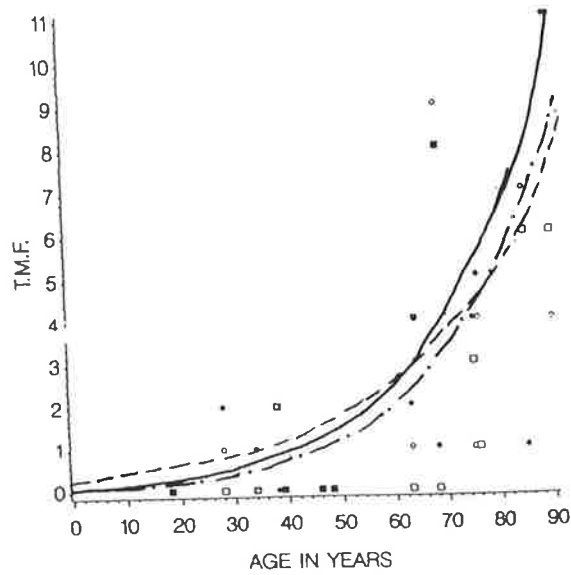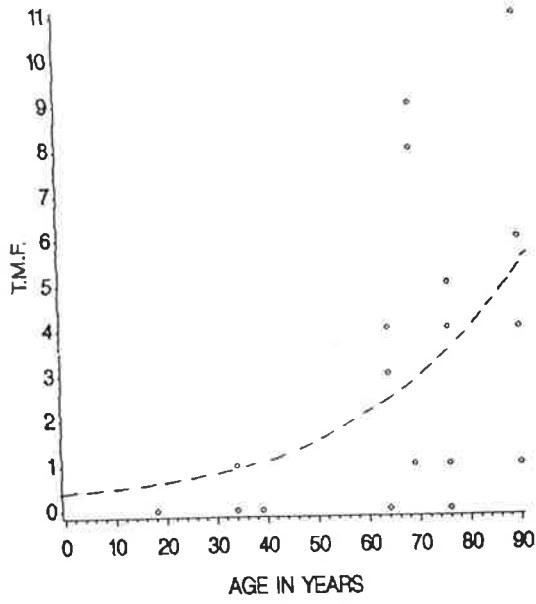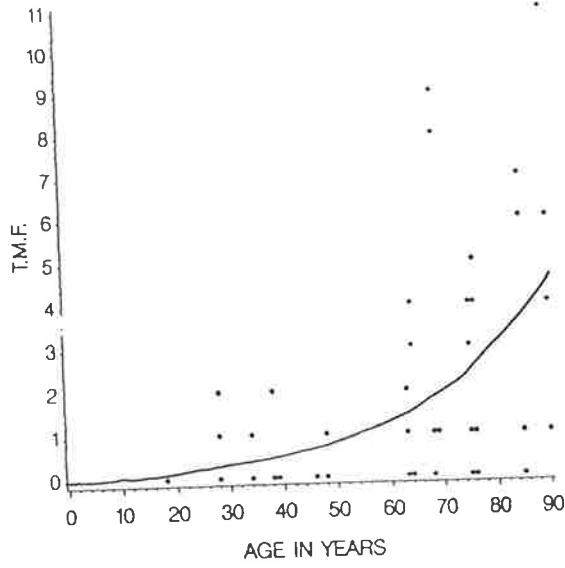
Figure 7.5 : Graph of trabecular thickness versus the number of healing trabecular microfractures in the total study group.

$$r = -0.4488, p < 0.01, n = 60$$

$$TMF = 6.42 - 0.04 \text{ Tb.Th}$$

Figure 7.6 : Graph of % mineralised bone (BV/TV) versus the number of healing trabecular microfractures in the total study group.

$$r = -0.3869, p < 0.01, n = 60$$

$$TMF = 5.78 - 0.14 \text{ BV/TV}$$

Figure 7.7 : Graph of % mineralised bone (BV/TV) versus the number of healing trabecular microfractures in the trochlea.

Medial Femur : $r = 0.0036$, $n = 15$. Not significant

$$TMF = 4.73 - 0.07 \text{ BV/TV}$$

Medial Tibia : $r = -0.2016$, $n = 15$. Not significant

$$TMF = 3.16 - 0.04 \text{ BV/TV}$$

Trochlea : $r = 0.5952$, $p < 0.05$, $n = 15$

O — — $TMF = 8.55 - 0.24 \text{ BV/TV}$

Patella : $r = -0.1310$, $n = 15$. Not significant

$$TMF = 0.34 - 0.004 \text{ BV/TV}$$

Figure 7.8 : Graph of the number of healing trabecular microfractures versus the total thickness of cartilage as measured from the decalcified sections from the opposite knee of the same individual in the total study group.

$$r = -0.4008, p < 0.01, n = 60$$

$$\text{Cartilage} = 2777.00 - 112.0\ \text{TMF}$$

Figure 7.9 : Graph of the number of healing trabecular microfractures versus the total thickness of cartilage as measured from the decalcified sections from the opposite knee of the same individual by region.

Medial Femur : $r = -0.6668, p < 0.01, n = 15$

● —— $\quad$ Cartilage = 2453.49 - 121.5 TMF

Medial Tibia : $r = -0.6439, p < 0.05, n = 15$

□ —·— $\quad$ Cartilage = 2883.56 - 176.5 TMF

Trochlea : $r = -0.2550, p > 0.20, n = 15$

Not plotted

Patella : $r = -0.2532, p > 0.20, n = 15$

Not plotted
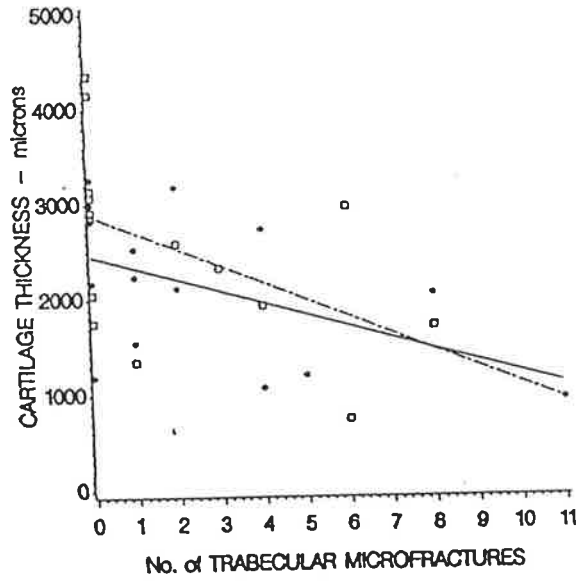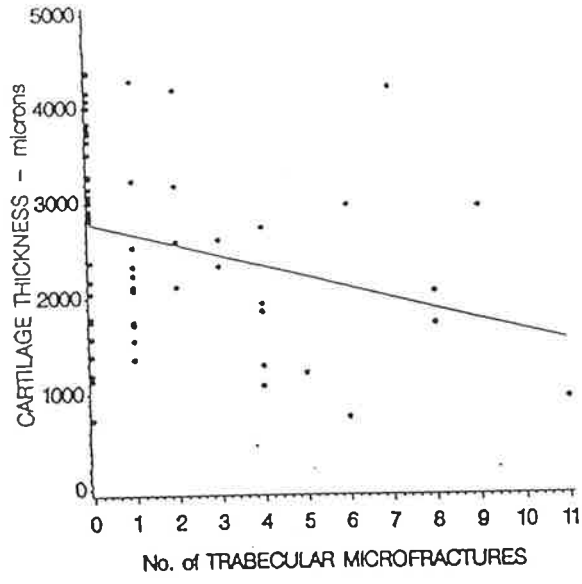
Figure 7.10 : A graph of the number of healing trabecular microfractures in the femur (TMF$_F$) versus the number of healing trabecular microfractures in the trochlea (TMF$_{Tr}$).

$r = 0.7253, p < 0.01, n = 15$

$TMF_{Tr} = 0.86 + 0.5 \, TMF_F$

Figure 7.11 : A graph of the number of healing trabecular microfractures in the femur (TMF$_F$) versus the number of healing trabecular microfractures in the tibia (TMF$_{Ti}$).

$r = 0.6394, p < 0.05, n = 15$

$TMF_{Ti} = 0.44 + 0.6 \, TMF_F$

Figure 7.12 : A graph of the number of healing trabecular microfractures in the tibia (TMF$_{Ti}$) versus the number of healing trabecular microfractures in the trochlea (TMF$_{Tr}$).

$r = 0.8718, p < 0.01, n = 15.$

$TMF_{Tr} + 0.41 + 0.9 \, TMF_{Ti}$
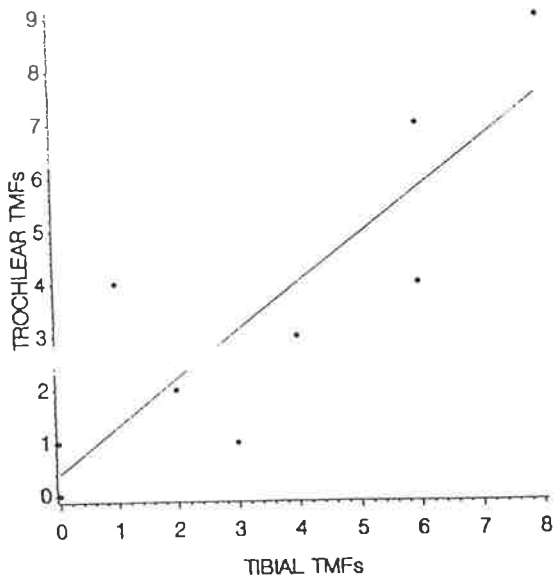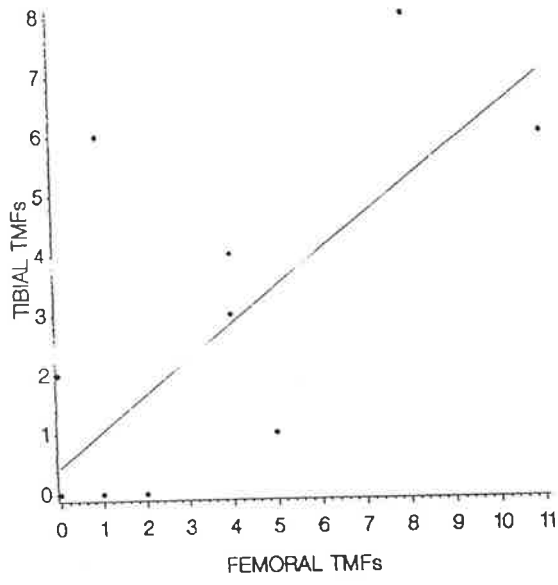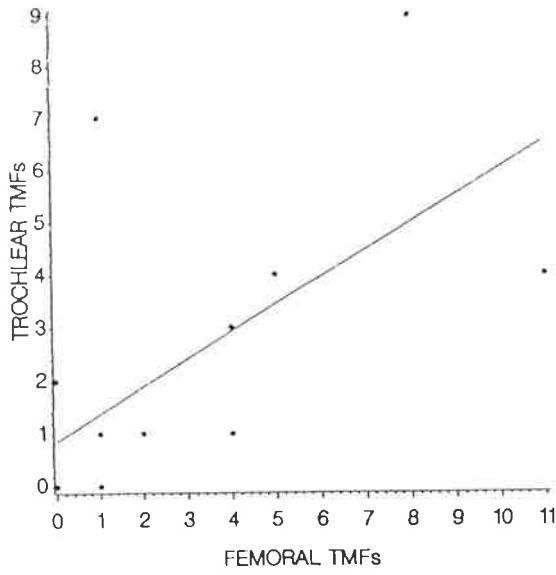
DISCUSSION

Healing trabecular microfractures have been described in the femoral head [17,27,36,39,138, 146,149,152], the acetabulum [102] and the lumbar vertebrae [142]. A previous radiographic study, examining the subchondral bone of the tibiofemoral joint, failed to find any healing trabecular microfractures [50]. The study examined specimens from patients who had undergone total knee replacement surgery for osteoarthritis, where the cancellous bone may become dense and trabecular microfractures hard to see. In a study examining the bony changes in chondromalacia patellae, Darracott and Vernon-Roberts [25] described nodular aggregates of woven bone on trabeculae within the patellae, but were unable to confirm that these aggregates represented callus formation. Subsequent studies by Radin [110], Vernon-Roberts and Pirie [142] and Urovitz [139] confirmed that these aggregates did, in fact, represent callus formation at the site of trabecular fracture.

The relationship between the number of healing trabecular microfractures and age, described before [36,142,149,152], has been confirmed by the present study. A number of reasons for this age-related increase in microfracture numbers have been put forward, including a proposed increase in the susceptibility of bone to fracture due to an increased incidence of metabolic bone disease in the ageing community [142]; the loss of bone mineral associated with ageing [149]; and a decrease in the rate of callus remodelling with increasing age as opposed to an increase in the rate of fracture [152].

The significant positive correlation between trabecular microfracture numbers and mean Tb.Th shown here has also been described previously [142,149,152]. This relationship explains the patterns of trabecular microfracture distribution seen in the composite maps. The area below the intercondyloid eminence in the tibia, the medial aspect of the medial femoral condyle, and the area of the trochlea furthest from the articular surface, are all areas characterised by an

open, fragile network of trabeculae (Figure 7.13). The paucity of trabecular microfractures in the patella may be explained by the fact that this is the area with the highest BV/TV and thickest trabeculae. Thus, the increased numbers of trabecular microfractures seen in the ageing population are the result of the decrease in BV/TV and Tb.Th with age described in Chapter 5. The fact remains, however, that the increase in microfracture numbers with age is exponential, whilst the fall in bone volume with increasing age is linear, suggesting that another factor may be responsible for the very rapid increase in microfracture numbers in later life. Possible factors would include a reduction in the degree of remodelling and healing, as has been previously suggested [152].

The close relation between the number of trabecular microfractures and the density of bone is confirmed by the relative paucity of microfractures in the patella, which has been shown in Chapter 5 to have a significantly greater BV/TV and thicker trabeculae than the other regions examined. This also explains the lack of any correlation between the number of microfractures in the patella and elsewhere in the knee.

Trabecular microfractures have been suggested as a mechanism by which bone remodels in response to functional demands [106]. Individual trabeculae within a cancellous bone network, will be exposed to forces sufficient to cause fracture during normal activity [106], until the trabecula is remodelled into position where it no longer is exposed to forces sufficient to cause fracture. The process of fracture and callus formation provides a stimulus by which osteoclasts and osteoblasts are recruited and remodelling may be initiated. The current study found a concentration of trabecular microfractures within certain areas of the four regions examined, yet remodelling of trabeculae is presumably not restricted to these areas, therefore microfracture is not the only mechanism by which remodelling of cancellous bone can be initiated. Microfracture is simply the result of progressive, age-related thinning of trabeculae to a point where the forces to which the cancellous bone is exposed in the course of normal activity are sufficient to cause fracture.

Figure 7.13 : Photograph of the macerated slices from the medial femur, medial tibia, trochlea and patella of a 72 year old male. Note the open, fragile trabecular network beneath the intercondyloid eminence of the tibia, and in the medial area of the femoral condyle.
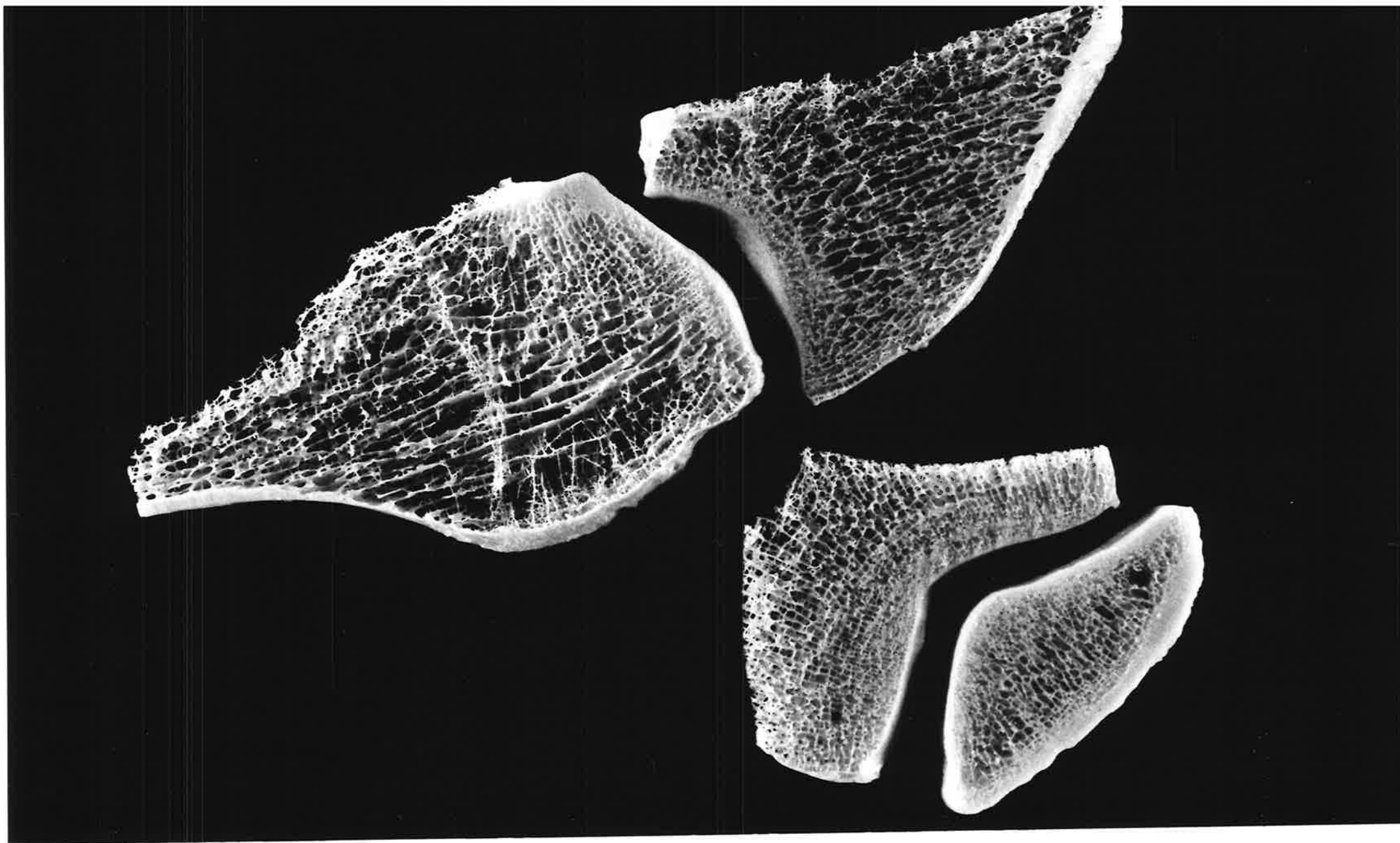
It has been proposed that the presence of trabecular microfractures within the cancellous bone acts to stiffen the bony network and expose cartilage to damaging forces [110,114]. There was no significant correlation found between cartilage condition, as assessed using the Mankin criteria on histological sections, and trabecular microfracture numbers. This is not entirely surprising in that the sections used to determine Mankin scores of cartilage condition were obtained from the opposite knee comprised only a fraction of the cartilage surface within each region and cannot be considered representative of the entire articular surface which has already been shown to have a wide variety of forms of cartilage change (Chapter 3). However, cartilage thickness has already been shown to be significantly related to the degree of degeneration, and trabecular microfracture numbers are related to the thickness of cartilage (Figures 7.8 and 7.9). Cartilage damage and trabecular microfracture may, however, appear related because they both exhibit significant correlations with age and the finding that trabecular microfracture numbers correlate significantly with cartilage thickness from the opposite cannot be considered conclusive evidence of a role for microfractures in the development of cartilage degeneration. An association between cartilage damage and the development of trabecular microfractures [110] has been found experimentally, but may simply be because they both represent forms of damage resulting from increased loading, rather than because increased bone stiffness due to the presence of healing microfractures acts to initiate cartilage damage. In fact, it is not clear why the presence of callus within a bony network should result in bone stiffening, since callus is comprised mainly of woven bone which is significantly less stiff than mature lamellar bone [19]. It is more likely that the presence of woven bone between the two ends of the fractured trabecula would act to increase bone compliance rather than to act as a mode of stiffening cancellous bone.

Although the presence of healing trabecular microfractures has been proposed to be a mechanism for cartilage damage, the findings of the present study do not support this hypothesis. It has already been shown that the patella is the

region with the earliest and most severe age-related cartilage changes, yet it is also the area with the fewest microfractures in the cancellous bony network. An inherent flaw in the microfracture hypothesis is that cartilage changes begin at a young age, when few microfractures are seen within the cancellous bone. This indicates that they are not an initiating factor in the development of age-related cartilage change, but that any association between cartilage condition and microfracture number is due to the effects of age.

CONCLUSIONS

1. There were no significant sex related differences in trabecular microfracture numbers, but the number of microfractures was significantly lower in the patella than in either the trochlea and the medial femur.

2. A significant increase in trabecular microfractures with age is described and is related to the age related decrease in BV/TV and Tb.Th.

3. A significant inverse relationship between trabecular microfracture numbers and cartilage thickness is described and may well be due to both factors being age-related.

4. Trabecular microfractures do not appear to have a role in the initiation of age-related cartilage damage.

CHAPTER 8 : CONCLUSION

Osteoarthritis is a common, painful and debilitating joint disorder, and much effort has been directed to understanding the development of the cartilage damage that is characteristic of this disease. Little work, however, has concentrated on the origin of the very similar cartilage changes seen in synovial joints with increasing age, and the unspoken assumption has been that their origin and nature are identical, but this point has never been specifically addressed.

The aim of this study, therefore, was to examine the evolution and nature of age-related changes within the knee, as well as examine a number of factors that have been proposed to play a role in osteoarthritic cartilage damage and to determine whether they have any role in the development of age-related changes

The specific objectives of this study were :

(1) To determine and quantitate the extent and severity of cartilage changes in the knee throughout adult life.

(2) To examine subchondral vascularity, calcified cartilage thickness, subchondral bone structure and trabecular microfractures - all of which have been proposed to play a role in the development of cartilage damage in osteoarthritis - and determine whether they have any role to play in the development of cartilage changes with increasing age.

(3) To determine whether regional variations in these same factors can explain any regional variations in cartilage condition with age.

In order to achieve these aims, intact knee joints including both the tibiofemoral and patellofemoral joints were obtained at autopsy from individuals

with no known history of bone or joint disease. There is a possibility that, although no patient had any record of joint disease, some may have had osteoarthritis but the diagnosis had not been made during life because they had not sought medical attention.

The design of the study divided specimens into two groups; Group 1 from which blocks for histology were obtained; and, Group 2, which allowed macroscopic assessment of subchondral vascularity and trabecular microfracture numbers. In retrospect, it would have been possible to dispense with Group 2 altogether since vascularity could have been assessed by a more rigourous histological technique, for example, using stereological methods involving either serial sections or sections taken from a number of levels within each block. Trabecular microfractures could have been assessed using a single slice taken from the same knee. This would have doubled the overall number of specimens assessed histologically but would have avoided the labour-intensive mapping of focal contacts. The principal benefit from this would have been that the time spent on the focal contact mapping could have been spent, instead, in including the lateral tibiofemoral compartment into the histological arm of the study. In view of the extensive changes seen in the posterior aspect of the lateral tibial facet, this could have provided more information on the development of advanced cartilage changes in the elderly. The specimens have, however, all been retained for future study. Notwithstanding these criticisms of the design, Group 2 did provide a method of assessing focal contacts throughout each articular surface and contributed some insight into the relationship between subchondral vascularity and cartilage condition.

8.1 The Pattern of Cartilage Damage

A number of previous studies have examined the range of cartilage damage within normal knees [2,4,7,15,32,61,63,84], but this was the first study to examine all regions of the knee, to utilise the Meachim Indian ink technique for highlighting early cartilage changes, and the direct contact mapping technique. This technique

represents a consistent, quantitative method for recording the nature and extent of cartilage changes within joints, without being biased by individual variations in anatomy, or distorted by the curved nature of the articular surfaces. The direct contact mapping technique may also be applied to osteoarthritic specimens in future work, and, for the first time, direct quantitative comparisons between the effects of ageing and of disease on the cartilage surface will be possible.

This study highlights the profound effect of age on cartilage condition within the knee. Advanced cartilage changes such as bone exposure, fibrocartilage and osteophyte formation appear as normal features of ageing and a completely intact articular surface is not seen in even the youngest and least degenerated specimens examined (Chapter 3). In the most degenerated specimens the difference between age-related changes and osteoarthritis becomes difficult, and it is clear that the presence of fibrocartilage, bone exposure or osteophytes cannot be considered diagnostic of joint disease. Any attempt at differentiation between the effects of age and the effects of disease on a joint must involve consideration of the age of the patient and the region of the knee involved. For example, bone exposure in even the most degenerated medial femur is not seen before the age group 85 to 94 (Figure 3.3), thus its presence before this age would be highly suggestive of the development of osteoarthritis. In contrast, bone exposure may develop in the patella as a normal part of ageing from the decade 65-74 and onwards (Figure 3.13). Only if it was present before this age could the presence of bone exposure be considered an indication of osteoarthritis within the patellofemoral joint.

Also highlighted is the fact that two opposing articular surfaces cannot be assumed to be equally affected by age-related cartilage changes. Although the differences in the frequency and severity of cartilage changes across the medial tibiofemoral joint may be influenced by the effects of the articulation of the patella on the anterior zone of the medial condyle this cannot explain the differences in cartilage condition across the lateral compartment. It is clear that the pattern and severity of cartilage change is not only defined by the loading forces acting on a

joint. The ability of a joint to deal with the potentially damaging forces is also dependant on the pattern of loading and on the mechanical properties of the various structural elements from which it is composed.

8.2 Factors related to cartilage condition

In assessing calcified cartilage thickness and other histologic features of the bone-cartilage interface and the cancellous bone, image analysis techniques were used, and this was the first study in which such techniques were used on specimens taken from opposing articular surfaces, and the first time that the irregularity of the tidemark and osteochondral junction had been measured.

The factors which have been hypothesized to play a role in the development of cartilage damage examined in this study were the number of focal contacts, the thickness of calcified cartilage, the bone-cartilage interface, the structure of the cancellous bone and the number of trabecular microfractures. To determine whether these factors played a role in the development of age-related cartilage change attempts were made to correlate them to the condition of the overlying cartilage.

In the case of histological specimens (Group 1), cartilage condition was determined on individual sections by using the Mankin grading system, and there was no significant correlation with any of the factors. This may be because the sections used were relatively small and possibly not representative

In Group 2 specimens, cartilage condition within the grid squares was assessed macroscopically, and it was found that squares with any form of cartilage change had significantly fewer focal contacts than squares with intact cartilage (Figure 6.5). A decrease in focal contact numbers is thus associated with a deterioration in cartilage condition and this would be consistent with the hypothesis that focal contacts provide nutrition to the deeper layers of cartilage and a decrease in their numbers and subsequently in nutrition will result in cartilage fibrillation. These findings are not conclusive since it can be argued that this association is a result of both factors being strongly correlated to age.

8.3 Factors related to age

The lack of any significant correlation between cartilage condition and either cancellous bone structure, the bone-cartilage interface or trabecular microfracture numbers may well be due to the non-representative nature of the sections used to determine Mankin Score. In an attempt to understand the origins of age-related cartilage change it may be of benefit to examine the age-related changes in the bone-cartilage interface, the cancellous bone, trabecular microfractures and focal contacts and determine whether such changes would be consistent with the effect of age on cartilage condition.

It has been proposed that the presence of large amounts of microcallus resulting from healing trabecular microfractures in the cancellous bone can decrease bone compliance and thus expose cartilage to damage [111,115]. This hypothesis does not explain the development of age-related cartilage changes since when such damage begins early in life, there are few trabecular microfractures in the cancellous network.

Focal contact numbers are highest in the young, but decrease rapidly in early adult life at a time when cartilage changes begin (Figure 6.1). This finding is consistent with the hypothesis that a fall in subchondral vascularity is related to the development of cartilage damage, presumably as a result of a decrease in nutrition to the deeper layers of hyaline cartilage. The irregularity of the osteochondral junction shows a significant exponential decrease in early adult life, and this is not surprising as this feature reflects the focal contact numbers present.

The fact that the thickness of the calcified cartilage layer remains constant throughout life argues against any changes in thickness being important in the development of age-related changes in the hyaline layer, but does not exclude the possibility that remodelling of the calcified layer and formation of the subchondral bone plate by focal contacts may have some role.

The number of tidemarks increases significantly with age, thus it can be proposed that the changes in cartilage with age are related to the reactivation of the calcification front. Any further discussion of this point depends on an understanding of the exact nature and function of the tidemark in the adult. It remains unclear, however, why reactivation of the tidemark requires duplication, especially since recent work has shown that a number of tidemarks may be metabolically active at one time [117]. It is possible that if tidemark activation is initiated by some yet to be defined product of cartilage breakdown diffusing from the surface, and as cartilage continues to breakdown, tidemark activation is repeatedly initiated.

The BV/TV of cancellous bone and the thickness of trabeculae both decrease with age in all regions of the knee examined, except for the patella in the case of BV/TV. It has been hypothesized that denser bone, that is with a greater BV/TV, thicker trabeculae and smaller trabecular spacing, is stiffer [151] and renders the overlying cartilage vulnerable to damage by no longer absorbing impulse loading forces [112,113]. The findings of this study are consistent with the hypothesis that high bone density and stiffness is associated with the development of cartilage damage; since bone stiffness is greatest in the young, the overlying cartilage will be most vulnerable early in adult life, which is when cartilage changes first appear.

Thus far, it would appear that of the factors which are proposed to play a role in the development of cartilage damage in osteoarthritis, only a decrease in subchondral vascularity and changes in the structure of the cancellous bone appear to be important in the development of age-related changes within the knee.

8.4 Factors related to regional differences

The third objective of this study was to determine whether regional differences in the bone-cartilage interface, the subchondral bone, subchondral vascularity or trabecular microfracture numbers could explain regional differences in cartilage condition within the knee.

From the direct contact mapping of the articular surfaces of the knee, it was found that the patella has less percentage area of intact cartilage than any other region within the knee, as well as larger percentage areas of slight, moderate and severe fibrillation and of fibrocartilage; thus the patella can be seen to be the area showing the most extensive age-related cartilage changes within the knee.

The patella does not differ significantly from other regions of the knee in terms of the numbers of focal contacts/mm^2, and the hypothesis that a decrease in focal contact numbers, and a decrease in cartilage nutrition may be related to age-related cartilage change cannot explain the development of extensive cartilage damage within the patella.

The patella is characterised by a higher BV/TV than the other regions examined, and unlike other regions of the knee the BV/TV of the patella does not decrease significantly with age. The patella has thicker trabeculae and smaller trabecular spacing than the other regions of the knee. Thus the cancellous network within the patella is denser than that seen elsewhere and remains so throughout life. The overlying cartilage is thus more vulnerable to damage from impulse loading forces at all ages. These results are consistent with the cancellous bone being of major importance in the development of age-related cartilage damage, since changes in cancellous bone density and structure are not only consistent with the development of cartilage degeneration with increasing age, but also regional variations in cartilage condition.

In contrast, although decreases in focal contact numbers may explain the development of age-related cartilage damage, they cannot explain the propensity of the patella to extensive cartilage damage.

The importance of cancellous bone in the development of age-related cartilage changes is supported by the fact that the bone beneath the posterior horn of the lateral meniscus is significantly denser than elsewhere in the tibia [45,58,59], and this is the area most frequently affected by progressive cartilage changes within the tibia. The findings of Byers et al [16] that progressive changes occur in weight

bearing areas may well be related to the fact that these areas have a higher BV/TV than non-weight bearing areas [36].

Other possible influences on cartilage condition which have not been examined in this study and which cannot be excluded from playing a role include biomechanical factors, biochemical and cellular factors within the cartilage, as well as inherited and environmental factors. It may also be the case that extensive cartilage changes within the patella are initiated by the high density of the underlying bone, but that their progression is accelerated by the high shear forces acting within the patellofemoral joint. Arguing against this is the fact that even within degenerated synovial joints the coefficient of friction is surprisingly low.

The cartilage damage difference not explained in terms of bone histomorphometric data is the male-female difference. It was seen in Chapter 3 that males have greater percentage areas of intact cartilage than females, and smaller percentage areas of moderate fibrillation, fibrocartilage, bone exposure and osteophytes. No significant male-female differences were found in the values for any of the cartilage or bone histological features examined. In fact, the greater decrease in BV/TV with age in females would suggest that they were less vulnerable to cartilage damage. Another factor, such as a sex-related difference in the mechanics of the knee joint itself, as described by Nissel et al [99] must be responsible for this difference. In support of this hypothesis it can be seen in this study that the frequency of advanced cartilage changes within the trochlea and patella tends to be greater in females (Table 3.1).

The findings of this study are consistent with the hypothesis that cancellous bone density and structure are important in the development of cartilage damage, since both age-related and regional variations in cartilage damage within the knee can be explained in terms of age-related and regional variations in bone structure.

The question whether bone changes precede changes in the hyaline cartilage is beyond the scope of a cross sectional study such as this, but it should be borne in mind that whilst it has been shown that bone responds to loading, and that cartilage damage can result from increased bone stiffness [106,115,116], the effect of cartilage breakdown on bone structure or mass has yet to be demonstrated.

8.5 Summary

It is concluded that :

(1) The cartilage changes seen in the knee with normal ageing include fibrocartilage, bone exposure and osteophyte formation and therefore these changes cannot be used as criteria for osteoarthritic change. The importance of region and age-matched controls in defining osteoarthritic joints is emphasised, since the disease may represent a premature development of normal age-related joint changes.

(2) The development of age-related cartilage changes cannot be explained in terms of the hypothesis that increased numbers of trabecular microfractures within cancellous bone increase bone stiffness and expose cartilage to damaging forces, since at the time that age-related cartilage changes begin, there are few microfractures present within the cancellous.

(3) Changes in the thickness of calcified zone of cartilage do not explain any age-related or regional differences in cartilage condition. Remodelling of the calcified layer and the subchondral plate by focal contacts may still be important in the development of cartilage changes.

(4) A fall in focal contact numbers with age can explain the age-related increase in cartilage degeneration, but the variations in the regional distribution of focal contacts cannot explain the regional differences in cartilage condition within the knee.

(5) Age-related and regional differences in the condition of cartilage can both be explained in terms of age-related and regional differences in bone histomorphometry. Thus, it is concluded that cancellous bone is a most important factor in the development of age-related cartilage damage within the knee.

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