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An ultrastructural study of the marginal transitional zone in the rabbit knee joint

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INTRODUCTION

The marginal transitional zone (marginal zone: Reyher, 1874) constitutes the circumferential boundary of articular cartilage in diarthrodial joints, where it is generally considered that cartilage, periosteum, synovial membrane and fibrous capsule merge. Apart from its intrinsic anatomical interest, the marginal zone with the underlying bone is of some significance in the pathology of arthritis. It is an early and common site of important morphological changes in osteoarthritis, such as osteophyte formation (Weichselbaum, 1877; Bennett, Waine & Bauer, 1942; McDevitt, Gilbertson & Muir, 1977). Proliferation of marginal soft tissue can also occur (Freeman & Meachim, 1979). This is particularly important in rheumatoid arthritis where it is associated with destruction of the cartilage periphery, especially where the soft tissue forms a pannus over the articular surface (Mills, 1970; Tateishi, 1973).

Synovium (synovial membrane) has been extensively studied with the light microscope (Key, 1932; Davies, 1943, 1946), the transmission electron microscope (Barland, Novikoff & Hamerman, 1962; Ghadially & Roy, 1966; Schumacher, 1969, 1975; Wright, Dowson & Kerr, 1973) and the scanning electron microscope (Shively & Van Sickle, 1977). Similarly, articular cartilage has been widely studied, particularly with the transmission electron microscope (Davies, Barnett, Cochrane & Palfrey, 1962; Weiss, Rosenberg & Helfet, 1968; Meachim & Stockwell, 1979).

Comparatively little recent research has been carried out on the marginal transitional zone. The marked vascularity of the synovium in the marginal zone was first noted by William Hunter (1743), who observed, "... there are a great number of arteries and veins which ramify into small branches and communicate with one and other by frequent anastomoses like those of the mesentery. This might be called the *circulus articuli vasculosus*, the vascular border of the joint." The vessels of the circulus articuli vasculosus terminate as dilated capillary loops overlying the margin of the articular surface (Toynbee, 1841), as shown by dye injection techniques (Key, 1932; Davies & Edwards, 1948; Scapinelli, 1968; Wladimirov, 1976).

While some light microscope studies have included the marginal zone (Benninghoff, 1925; Key, 1932; Wolf, 1974*a*, *b*) only Tateishi (1973), using pathological (rheumatoid) material, has investigated its ultrastructure. Ultrastructural features of the normal rabbit marginal transitional zone are now described.

MATERIALS AND METHODS

Six male New Zealand white rabbits (*Oryctolagus cuniculus*) were used. Skeletal maturity was assessed histologically by reference to the growth plate, subchondral bone and cartilage of the femora. Two early immature rabbits (1·5 kg, 1·6 kg), two late immature rabbits (2·5 kg, 2·7 kg) and two mature rabbits (3·6 kg, 3·7 kg) were used, these categories corresponding to those of previous workers (Thompson & Bassett, 1970; Ogata, Whiteside & Lesker, 1978). Each rabbit was stunned and killed by cervical dislocation. Thin tissue slices of the marginal zone, with adjacent synovium, articular cartilage and underlying tissues were taken from the medial margins of the patellar area and medial condyle of the left femur. The site of origin and orientation of each tissue slice was noted. Tissue slices were placed in fixative within six minutes of death. In most cases 5% glutaraldehyde in Palade sucrose buffer pH 7·4 at 4 °C was used, but specimens from one rabbit (2·7 kg) were fixed in 2% osmium tetroxide in Palade sucrose buffer pH 7·4.

After primary fixation in 5% glutaraldehyde and post-fixation in 2% osmium tetroxide the tissues were dehydrated in absolute alcohol and embedded in Araldite. Semithin, 1 μm sections were cut from the tissue radial to the articular circumference (i.e. across the marginal zone) using a Reichert OmU3 ultramicrotome fitted with a glass knife. Sections collected on to a glass slide and stained by toluidine blue (Ito & Winchester, 1963) were examined with the light microscope. Thin sections were cut with a diamond knife, collected on copper grids, stained with uranyl acetate and lead citrate and examined in a Philips EM301 transmission electron microscope at 60 kV.

RESULTS

Both methods of fixation appeared to yield satisfactory tissue preservation. At low magnifications the marginal zone consisted of vascular synovium and avascular cartilage, which were easily distinguishable from each other. The cartilage had a convex margin and the synovial membrane abutted on and partly overlapped the cartilage (Figs. 1, 2). Both marginal sites sampled in the joint showed the same structure. No differences between late immature and adult specimens were observed. Features peculiar to early immature animals are noted below under the relevant heading.

Surface of the marginal synovium

The marginal synovium comprised a distinct surface layer and deeper tissue within which cells and blood vessels could be found. The surface layer (Fig. 3) could be subdivided into three laminae totalling 1 μm in thickness. The superficial lamina, of patchy electron-dense material bordering the synovial cavity, adjoined an intermediate lamina, of finely fibrillar structure and moderate electron density, containing a few transversely sectioned collagen fibrils and sometimes the processes of synovial intimal cells. The deep lamina contained collagen fibrils cut both longitudinally and transversely. The surface of the marginal zone, which was fairly smooth, merged imperceptibly with the surface of the articular cartilage, which was of a similar texture. At the other end, it was continuous with the surface of the synovium generally, which appeared disrupted by comparison.

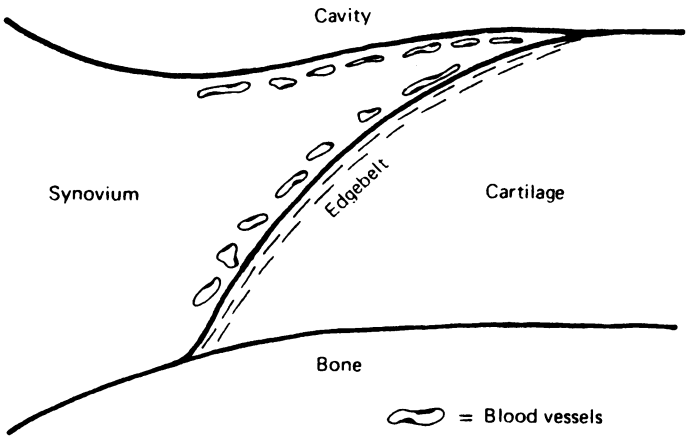


Fig. 1. Diagram of the marginal zone of rabbit articular cartilage.

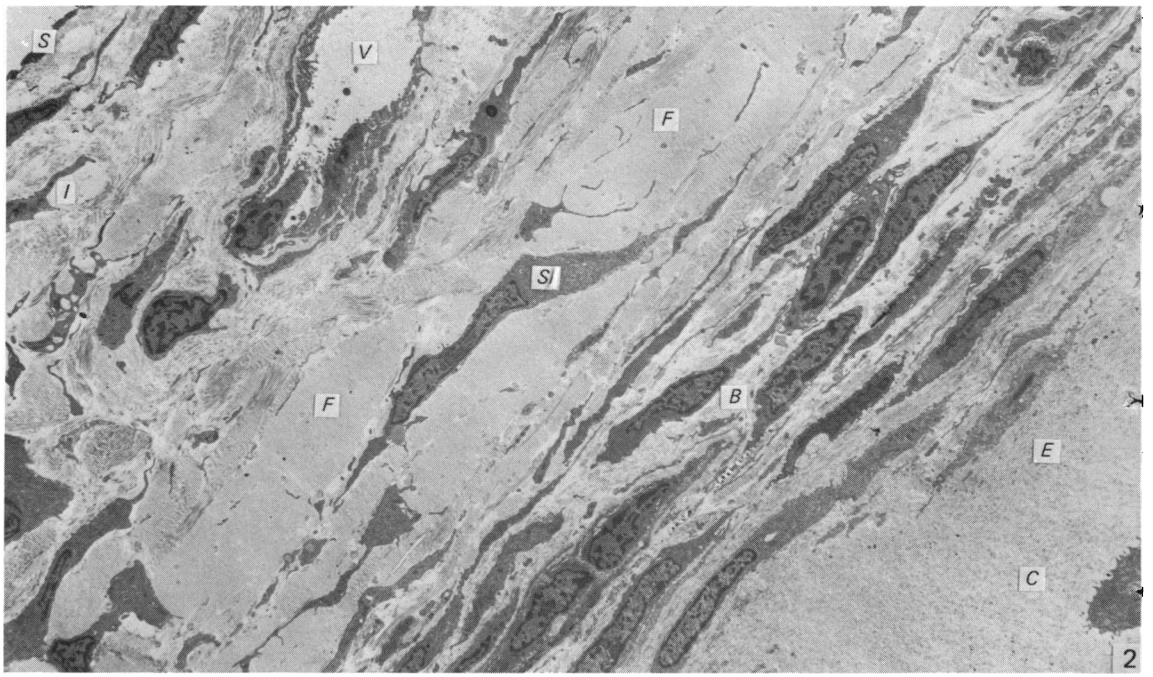
Cells of the marginal synovium

The matrix of the deeper marginal synovial tissue consisted largely of collagen fibrils with a little elastic tissue, lying amongst amorphous material. Within this matrix there were four categories of synovial cells: intimal cells, subintimal cells, boundary cells and cells associated with blood vessels (Fig. 2).

Discoidal intimal cells, flattened in a plane tangential to the synovial surface, lay immediately beneath the surface layer. There were two or three strata of these cells at the synovial end of the marginal zone, reducing to a single layer near the articular cartilage surface, where they resembled superficial chondrocytes. There appeared to be three types of intimal cells. Type 'A' cells were characterised by prominent Golgi areas, numerous pinocytotic vesicles, and scanty granular endoplasmic reticulum (ER). Type 'B' cells contained profuse granular endoplasmic reticulum, but sparse Golgi membranes and few pinocytotic vesicles. An intermediate type of cell (Fig. 4), which contained both Golgi apparatus and granular endoplasmic reticulum, was most frequently identified; type B cells outnumbered type A cells. In a few cells, a thin fibrous lamina underlay the nuclear envelope: in such nuclei, the chromatin was pale and uniformly distributed, in contrast to the clumped, marginated chromatin in the nuclei of other intimal cells. Filopodia were more common on the deep than the superficial aspect of cells near the synovial surface.

Subintimal cells (*c.* 8 μm long) were similarly flattened tangential to the synovial surface. Each cell possessed short (*c.* 0·6 μm) filopodia arranged peritrichously and a few long, branching filopodia (up to 20 μm long) projecting from the poles of the cell (Figs. 2, 5). These formed a wide three dimensional net, with collagen fibrils lying in its interstices. Subintimal cells contained a flattened nucleus (6 μm long) with clumped marginated chromatin and a nucleolus. Myelin figures and fat droplets were often present in their sparse cytoplasm in addition to the normal organelles.

Near the synovium/cartilage junction, subintimal cells were replaced by one to four layers of boundary cells (Figs. 2, 6). Boundary cells were more rounded, with only a few short filopodia, and contained more cytoplasmic organelles than the subintimal cells. Due to the abrupt change from synovial to cartilage tissue, the inner layer of synovial boundary cells were in contact with cartilage matrix on their deep surface and lay close to chondrocytes. Where a longitudinally sectioned collagen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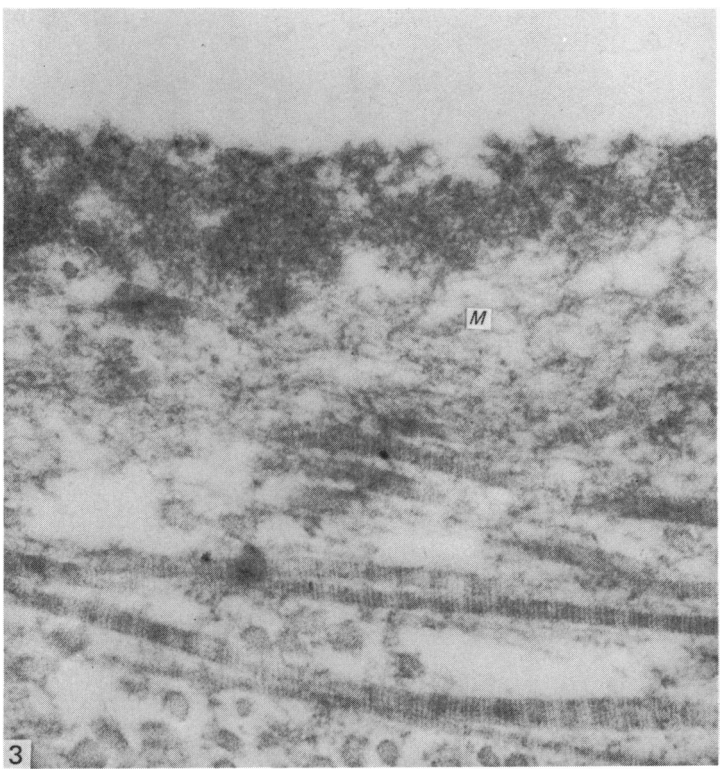
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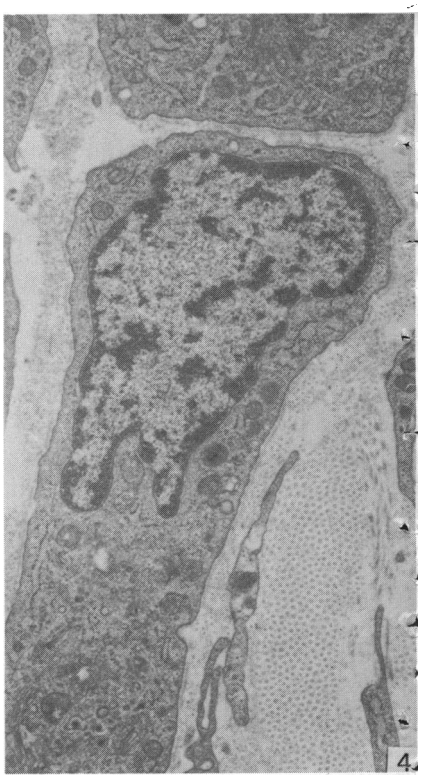
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bundle ran from the synovium into the cartilage, the boundary cells were few or absent and hence the morphological change from subintimal cell to chondrocyte could be more abrupt (Fig. 7). At the intimal lining, an extremely gradual morphological change in the superficial cells occurred on passing from synovium to cartilage. This made the site of transition from synovium to cartilage more difficult to locate near the surface.

Blood vessels were particularly numerous in early immature rabbits. The vessels, sectioned transversely, obliquely or longitudinally, were located exclusively within the synovium (Figs. 1, 2). They formed a superficial stratum just beneath the synovial surface, and a deep stratum situated just superficial to the sloping boundary of the marginal cartilage (Fig. 1). The superficial vessels extended further towards the middle of the articular area than the deep vessels. All were type I non-fenestrated capillaries with low endothelium and pericytes, and were of wide bore (6·5–10 μm diameter (Fig. 8)). The low endothelium (typically 500 nm thick) was surrounded by three to four discontinuous layers of basal lamina. Endothelial nuclei were evenly distributed around the capillary circumference. Many short cell processes projected into the lumen and the large number of pinocytotic vesicles gave the endothelial cells a foamy appearance. Contiguous surfaces of adjacent endothelial cells interdigitated or overlapped in places where the endothelium was particularly thin, with occasional junctional complexes.

Pericytes (Fig. 8) were enclosed by endothelial basal laminae and also contained many pinocytotic vesicles. Each pericyte sent out foot processes towards the endothelial cells; these bifurcated into long thin filopodia which formed a discontinuous layer within the basal lamina. No junctional complexes between pericytes and endothelial cells were observed. One to five flattened subintimal cells (Fig. 8) were often arranged concentrically around the capillary, external to the basal lamina. Pinocytotic vesicles, but few other organelles or inclusions, were prominent in these cells.

No mast cell, histiocyte, lymphocyte, nor any nerve, nerve ending or lymphatic vessel was observed in the marginal zone synovium.

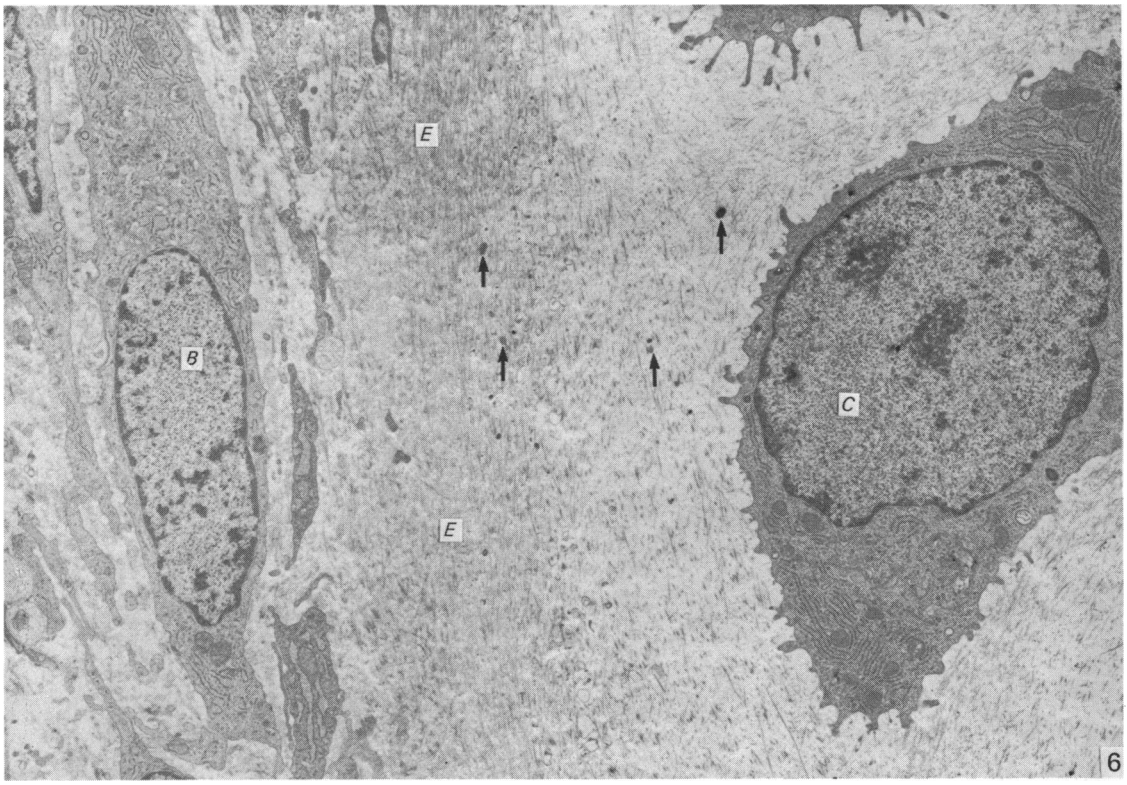
Cells of the marginal cartilage

The marginal zone cartilage contained scattered chondrocytes in a collagenous matrix. The matrix appeared homogeneous in early immature tissue. In late immature and mature tissue, the lacunae consisted of finely textured pericellular matrix often devoid of cross-banded collagen fibrils; the surrounding matrix contained many collagen fibrils which became thicker and coarser with increasing distance from the cell. Electron-dense matrix vesicles were present in the coarsely fibrous matrix of more mature specimens (Fig. 6).

Fig. 2. Part of the marginal zone where synovium overlaps the articular cartilage (*C*). Intimal cells (*I*) and a blood vessel (*V*) lie beneath the synovial surface (*S*) and subintimal cells (*SI*) are situated among the large masses of collagen fibrils (*F*) which are mostly cut transversely. Several layers of synovial boundary cells (*B*) adjoin the cartilage matrix. *E*, position of edge-belt. Late immature animal. Glutaraldehyde. × 2000.

Fig. 3. Synovial surface of marginal zone. Electron-dense amorphous material forms a superficial lamina. Finely fibrillar material (*M*) intervenes between the superficial lamina and a deep lamina containing many collagen fibrils. Mature animal. Glutaraldehyde. × 84000.

Fig. 4. Parts of two synovial intimal cells of the intermediate type. Late immature animal. Glutaraldehyde. × 9000.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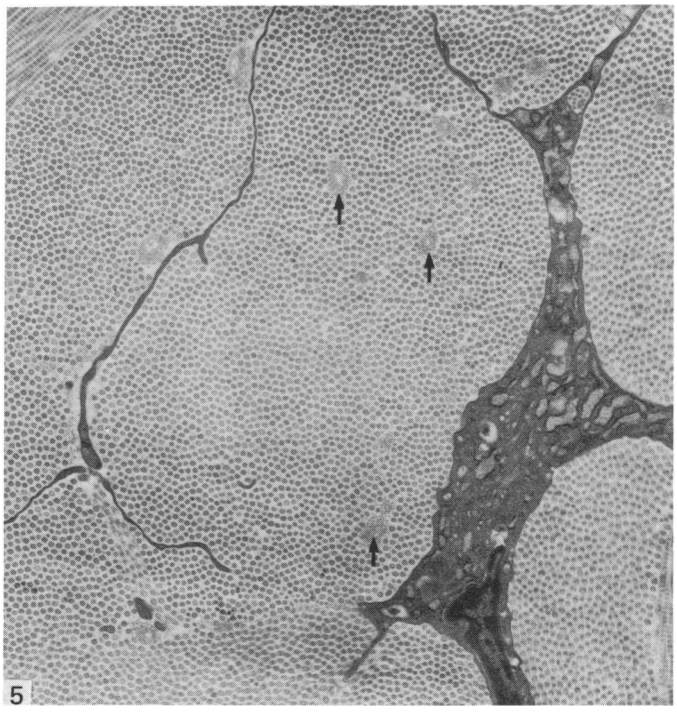
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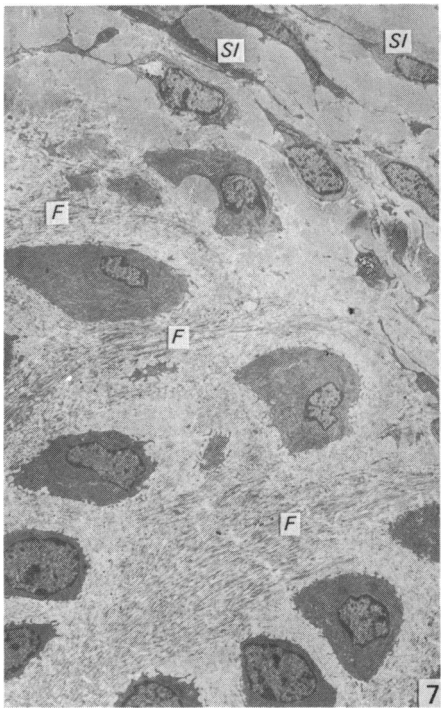
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Near the synovium/cartilage interface the chondrocytes were slightly more flattened. In early immature animals only, collagen bundles ran from the synovium into the cartilage and divided the chondrocytes into columns whose long axis lay perpendicular to the junction (Fig. 7). The cells were slightly flattened, with fewer cell processes on the sides adjacent to the fibril bundles, and had nuclei *c.* 4 μm in diameter. They sometimes lay in pairs within the columns, perhaps indicating that mitosis had recently occurred. Granular endoplasmic reticulum was particularly prominent in the cytoplasm.

No cell other than chondrocytes, nor any blood vessel, nerve, lymphatic or cartilage canal was observed in the marginal zone cartilage.

Marginal zone collagen

Collagen fibrils occupied much of the synovium and cartilage of the marginal zone (Fig. 2). In the cartilage within 10 μm of the junction most fibrils were orientated tangential to the synovium/cartilage interface, forming an 'edge-belt' running obliquely from articular surface to the bone (Figs. 1, 2, 6). In the synovium, transversely sectioned fibrils predominated (Figs. 2, 5), the sparse longitudinally sectioned bundles forming a coarse mesh around the transverse collagen.

Collagen of the marginal synovium

The longitudinal bundles of collagen fibrils lay in different strata tangential to the surface of the synovium and, except in early immature animals, inserted into the cartilage edge-belt. The deep lamina of the surface layer merged with the most superficial stratum, and there were up to five strata situated more deeply, each profile of a stratum containing about 10–30 fibrils (Fig. 9). Interlinking bundles of a similar size passed between the deeper longitudinal bundles but did not connect with the superficial stratum. Close to the periphery of the articular cartilage, the most superficial bundle became continuous with the collagen of the articular surface, itself a continuation of the edge-belt.

Nevertheless, much the greater proportion of the synovial collagen was transversely sectioned (Figs. 2, 5, 7, 9), subdivided into groups of several hundred fibrils by the filopodia of the subintimal cells. Towards the articular end, the intersecting filopodia were replaced by the interlinking bundles of longitudinal collagen. In addition, short bundles, containing about 25 collagen fibrils in the plane of the section, joined adjacent groups of transversely sectioned collagen throughout the synovium. Regardless of the animals' maturity, collagen fibrils had much the same range of diameter (10–60 nm) and were interconnected by fine filaments. Short, thin, aperiodic

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Fig. 5. Parts of two synovial subintimal cells. Long filopodia partly separate transversely sectioned (circumferential) groups of collagen fibrils. The small bundles of microfibrils (arrows) exhibit no periodicity when observed in longitudinal section and probably surround elastin. Late immature animal. Glutaraldehyde. × 11000.

Fig. 6. Synovium/cartilage junction showing part of the fibrous edge-belt (*E*) in the periphery of the cartilage, intervening between a chondrocyte (*C*) and boundary cells (*B*). There are matrix vesicles (arrows) in and near the edge-belt. Late immature animal. Glutaraldehyde. × 6000.

Fig. 7. Synovium/cartilage junction in an early immature rabbit. Short columns of chondrocytes are separated by bundles of collagen fibrils (*F*) running from the synovium. In this actively growing animal there is no well-defined edge-belt, nor is there a synovial boundary cell layer distinct from the subintimal cells (*SI*) in the transversely sectioned collagen. Glutaraldehyde. × 1500.

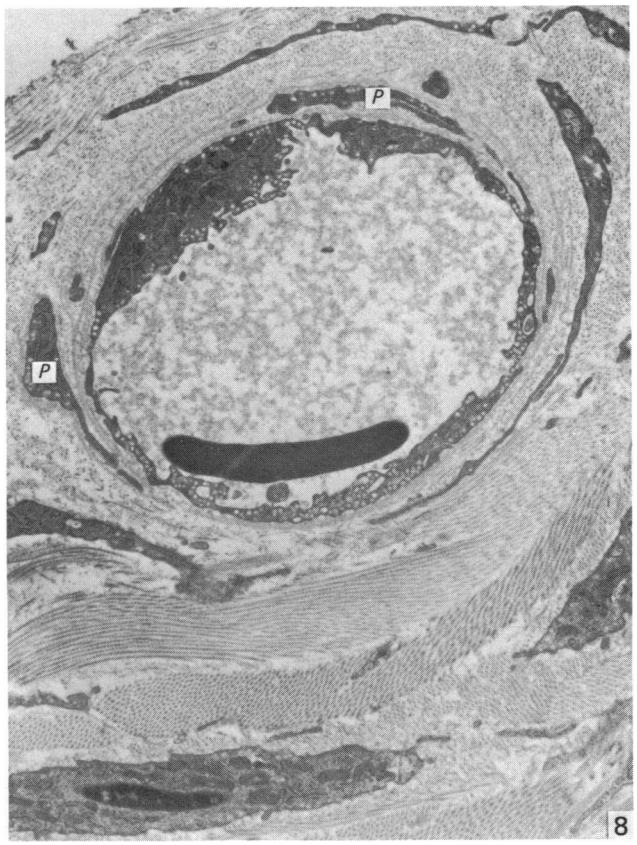

Fig. 8. A type I capillary with non-fenestrated endothelium and numerous pinocytotic vesicles, just beneath the synovial surface. Pericytes (*P*), enclosed by basal laminae, and other perivascular cells surround the vessel. Early immature animal. Glutaraldehyde. × 8000.

bundles of microfibrils (Fig. 5), probably elastic tissue, were observed throughout the marginal zone synovium but not in the cartilage. They often lay within, but had no constant relationship to, collagen bundles.

Marginal cartilage collagen

In the marginal cartilage (Fig. 6), short, spindle-shaped profiles of collagen fibrils of various widths accounted for much of the matrix. They were randomly orientated except in the edge-belt. Longitudinal collagen bundles from the synovium pierced the synovium/cartilage junction and inserted into, but did not penetrate further than, the edge-belt in adult animals.

DISCUSSION

The structure and composition of the marginal zone of the rabbit knee joint agrees in general with classical descriptions (Hunter, 1743; Key, 1932). Although it is not merely a juxtaposition of synovium and cartilage, previous investigations of these two tissues are relevant to the present study.

The surface layer observed in the marginal synovium bears some resemblance to one form of articular cartilage surface depicted by Meachim & Stockwell (1979).

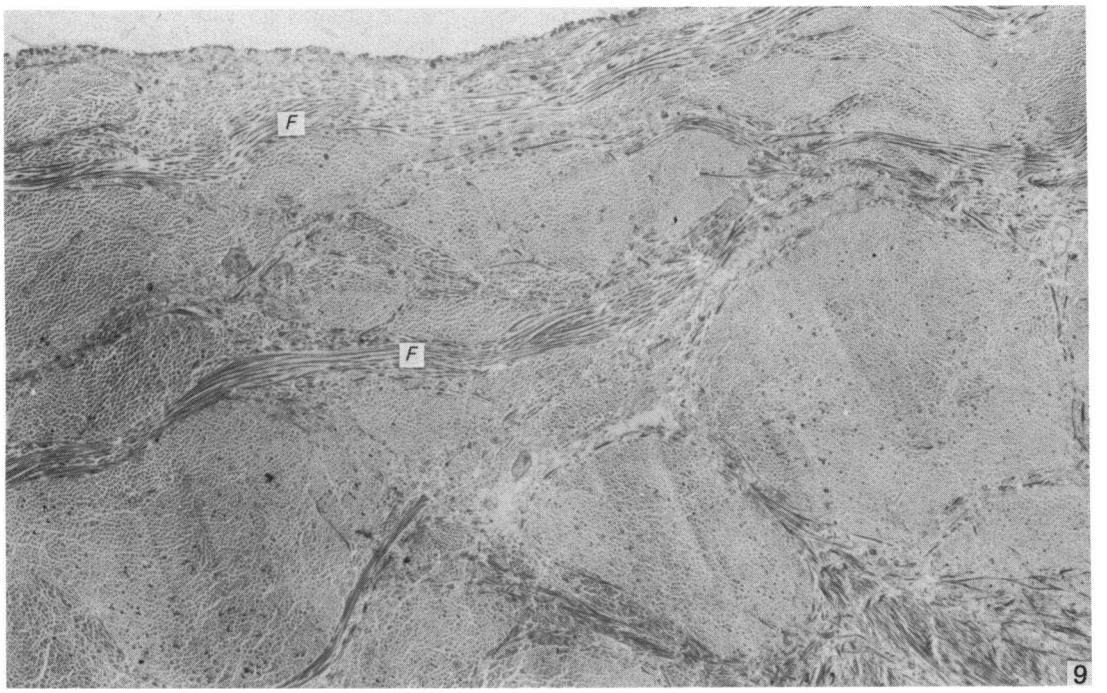

Fig. 9. An acellular region of the superficial part of the marginal synovium. Two longitudinal (radial) strata of collagen fibrils (*F*) lie between transversely sectioned (circumferential) collagen bundles. Mature animal. Osmium tetroxide. × 5000.

It is much smoother than the irregular surface noted in most synovial membrane (Ghadially & Roy, 1966; Weiss *et al.* 1968; Wolf, 1974*a*, *b*; Schumacher, 1975) although the features of the deeper tissue of the surface layer are similar. Possibly, the roughened surface of most synovium is due to the wear and tear of joint movement. The electron-dense material at the surface may correspond to deeply staining anionic substances noted previously (Davies, 1946), probably hyaluronate–protein complexes.

Intimal cells in the marginal synovium are similar to those in synovium generally (Ghadially & Roy, 1966; Wright *et al.* 1973; Wolf, 1974*a*, *b*; Schumacher, 1975) although they are not linked by tight junctions or desmosomes. Subdivisions into A and B cell profiles were confirmed, although intermediate types predominate in the marginal tissue. Such synovial cells can secrete degradative enzymes such as collagenase and hyaluronidase (Glynn, 1977; Jubb, 1980). Hence, the anatomical position of marginal cells may give them a specific role in pannus formation and in other changes of rheumatoid synovium (McGuire, Meats & Russell, 1980). As in the guinea-pig (Ghadially & Roy, 1966), rabbit type A cells also exhibit prominent pinocytosis.

The fibrocytic nature of the subintimal cells indicates that they produce the extracellular fibrils of the marginal zone. The prevalence of myelin figures, particularly in older animals, may be associated with cell degeneration. Macrophages and mast cells were not identified although present in the looser subintimal tissue of synovium elsewhere (Davies, 1946; Schumacher, 1975). Ultrastructural observation confirms the gradual transition from synovial cell to chondrocyte in the marginal zone noted by light microscopy (Reyher, 1874; Key, 1932; Davies, 1946; Wolf, 1974*a*), the

chief reason for the abrupt nature of the synovium/cartilage boundary being the disposition and density of cells and collagen fibrils. The form and position of the boundary cells suggest a perichondrial role.

In immature human joints, capillaries pass from the marginal synovium into the cartilage (Scapinelli, 1968; Wladimirov, 1976), but the cartilage in all rabbits in the present study is avascular. This concerns the possible sources of nutrition of this region (Davies & Edwards, 1948; Scapinelli, 1968; Wladimirov, 1976), the species difference in vasculature during development relating to the different thicknesses of rabbit and human cartilage. The cartilage layer, consisting of true articular and as yet unossified epiphyseal cartilage, is thin in the rabbit and could be adequately nourished by diffusion from synovial fluid, from subchondral marrow spaces and from vessels in the marginal synovium. In the thicker cartilage of man, vascular canals penetrating the cartilage from the marginal zone are presumably required in addition. Further work may clarify the relative importance of these sources. The wide bore and distribution of vessels resemble these features in human marginal synovium, and the variety of vascular profiles is compatible with capillary loops (Toynbee, 1841; Davies, 1946; Wladimirov, 1976).

Earlier workers have variously designated synovial capillaries as type II with fenestrated endothelium (Wright *et al.* 1973; Schumacher, 1969, 1975) or as both type I and type II (Dryll *et al.* 1977). Marginal zone capillaries are non-fenestrated (type I) in the rabbit, and hence there is no evidence for an enhancement of the passage of fluid and electrolytes towards the overlying synovial surface, as adduced from observed preferential orientations of fenestrae towards the synovial surface in earlier studies (Ghadially & Roy, 1966; Wright *et al.* 1973; Schumacher, 1969, 1975; Dryll *et al.* 1977). Without doubt, the synovial membrane elsewhere supplies sufficient synovial fluid, although intense pinocytotic activity in the endothelium, pericytes and surrounding subintimal cells of the marginal synovium indicates a substantial exchange of substances with the surrounding tissue. According to Tateishi (1973) the pericytes and concentric subintimal cells could contribute to the inflammation of the marginal synovium seen during osteophyte and rheumatoid pannus formation.

Vasomotor and vasosensory nerves, and possible mechanoreceptors are found in synovial membrane generally (Key, 1932; Davies, 1946; Gardner, 1948, 1953; Schumacher, 1975). These may be absent from the marginal synovium, partly because no blood vessels larger than capillaries are present and also because mechanical stresses are thought to be minimal here (Marshall, 1969). Lymphatic drainage of the synovium (Schumacher, 1975) does not appear to extend into the marginal zone.

Marginal zone chondrocytes are similar to zone II (middle zone) cells (Weiss *et al.* 1968; Stockwell & Meachim, 1979) of articular cartilage generally. Near the articular surface, the chondrocytes next to the synovium/cartilage junction resemble zone I (superficial zone) cells, but deeper marginal chondrocytes, however far from the articular surface, nevertheless exhibit the features of zone II cells. Thus, the morphological features of its deeper chondrocytes are related more to the proximity of the synovium/cartilage boundary than to the distance from the articular surface proper.

The outstanding feature of electron micrographs of the marginal synovium of the rabbit knee joint is that the majority of collagen fibrils are transversely sectioned. This implies that they run around the perimeter of the articular cartilage for some distance. The results of studies with polarised light (Benninghoff, 1925 and reiterated

in authoritative reviews, e.g. Bennett *et al.* 1942), have hitherto emphasised a predominantly radial orientation of the collagen with respect to the articular circumference. The present study shows that, in the rabbit, radial (longitudinally sectioned) fibrils are in the minority in the synovium. This may be because the fibrous capsule of the rabbit knee joint inserts some millimetres from the marginal zone (A. M. Thompson, unpublished observation), into the periosteum (mature animals) or growth plate (immature animals). Hence, the synovium is probably not normally subjected to traction radial to the articular margin (Marshall, 1969). Indeed, it is difficult to identify the source of a circumferential tensile stress which might act as a stimulus for the main fibre orientation. It seems that the circumferential collagen bundles are arranged in an analogous fashion to the string tied around the top of a rimmed jam jar, holding down a cellophane cover. While they may resist any tendency of the cartilage to swell radially, it is proposed that they function principally as a retaining band for the synovium nearest the articular margin. This would prevent synovial tissue herniating on to the articular surface, where it could suffer injury. The cartilage edge-belt, which is continuous with the collagenous 'tension-resisting diaphragm' in the superficial zone of the articular cartilage, presumably exists to withstand tensile stresses created in the marginal zone by forces acting on the articular surface (Benninghoff, 1925).

When viewed with the electron microscope the deeper radial synovial collagen did not appear to be a direct continuation of the cartilage collagen as depicted by Bennett *et al.* (1942); the discontinuity could easily have been overlooked using light microscopy alone. On the other hand, the continuity between the most superficial radial synovial collagen and the collagen of the articular surface, earlier noted by Benninghoff (1925) and by Weiss *et al.* (1968), was confirmed. Wolf (1974*a*, *b*) proposes a 'chondro-synovial membrane' at the surface, forming an uninterrupted lining to the joint cavity.

The coarse mesh formed by the deeper radial synovial collagen may serve to knit the circumferential collagen bundles together. The insertion of this coarse mesh into the articular cartilage edge-belt should help to anchor the circumferential collagen to the articular margin.

SUMMARY

The ultrastructure of the marginal transitional zone of femoral articular cartilage has been studied in the rabbit knee.

There is an abrupt boundary between the convex margin of the cartilage and the synovial membrane. This is due to the arrangement and amount of collagen and of cells, because cell ultrastructure changes gradually from synovium to cartilage. The densely fibrous marginal synovium contains scattered fibrocytic cells with sparse cytoplasm and long filopodia. Near the synovium/cartilage interface, oval boundary cells containing more abundant cytoplasm abut on the cartilage matrix. In the periphery of the cartilage, an edge-belt of collagen fibrils runs obliquely from articular surface to subchondral bone. Chondrocytes near the edge-belt, whatever their depth from the articular surface, ultrastructurally resemble middle zone (zone II) cells of articular cartilage generally.

The synovial surface of the marginal zone is smooth and resembles articular cartilage surfaces. Most intimal cells contain plentiful granular endoplasmic reticulum and Golgi membranes and hence are intermediate between A and B synoviocytes commonly found elsewhere. Non-fenestrated (type I) capillaries lie in a superficial

stratum beneath the synovial surface and in a deep stratum near the synovium/cartilage boundary, and are surrounded by pericytes.

No mast cells, macrophages, lymph vessels or nerves could be identified in the marginal zone.

Contrary to earlier accounts of collagen orientation in this zone, most of the fibrils in the marginal synovium appear to run around the perimeter of the cartilage and only a few bundles run radially from the synovium towards the cartilage. It is suggested that the circumferential collagen both contains the marginal cartilage and prevents displacement of synovial tissue on to the articular surface. The radial strata of collagen serve to anchor the circumferential collagen to the cartilage edge-belt. In agreement with earlier investigators, it is considered that the edge-belt withstands tensile stresses arising from deformation of the articular surface. The role of the marginal synovium is also discussed in relation to synovial fluid formation and cartilage nutrition.

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