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Synoviocytes

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The importance of the synoviocytes both in the physiology of normal joints and in the breakdown of articular cartilage in many forms of arthritis has long been recognised, but their activities and potentialities are not yet fully understood.

The normal functions of the synoviocytes include the secretion of hyaluronic acid into the synovial fluid, the removal of solid particles from the joint cavity, and the activation of plasminogen (Berger, 1977) which is thought to prevent the accumulation of fibrin in the joint. There are several different kinds of cell in the synovium, however, and it is uncertain which types are responsible for these various functions.

In inflammatory arthritis the synovium becomes greatly enlarged, mainly owing to heavy infiltration by lymphocytes and plasma cells, and invades the cartilage, which it gradually replaces. The relative importance of the synoviocytes, the chondrocytes, and the inflammatory cells in this destructive process is not known. In osteoarthrosis, at least in the early stages, there is no inflammation, and it was assumed that the disintegration of the cartilage in this disease was caused simply by wear and tear. More recently it has been shown that one of the earliest changes in osteoarthrosis is loss of proteoglycan from the cartilage matrix accompanied by an increased rate of synthesis of this compound (McElligott and Collins, 1960; Collins and McElligott, 1960). This suggests that mechanical damage may be secondary to biochemical alterations in the cartilage and the possibility that the synoviocytes may play some part in causing these primary biochemical changes cannot be excluded.

During the past few years my collaborators and I have studied the synovium from the following points of view: (1) the morphology of the normal synovium, as a basis for experimental studies; (2) the nature and relationship of the various types of synoviocyte; and (3) the capacity of the synovium to degrade cartilage matrix in the absence of inflammatory cells. The tissues of the metacarpophalangeal joints of young pigs aged about 6 weeks to 3 months have been used, and experiments have been made by organ culture and cell culture methods. In this communication our main findings are briefly reviewed in relation to existing knowledge.

Normal morphology of the synovium

The morphology of the synovium varies widely in different joints and in different regions of the same joint. It consists of a lining layer (Fig. 1), the intima, usually 1-3 cells in thickness resting on a very vascular subintimal tissue which may be adipose, fibrous, or areolar according to its site. In the metacarpophalangeal joint of the pig (Fell *et al.*, 1976) there is very little adipose tissue. There is much more in the larger joints. In places the synovium is extended into villi which project into the joint cavity.

Attention has been mainly directed to the intima since Barland *et al.* (1962), in an electron microscopy study of this layer, found two cell types—phagocytic cells resembling macrophages, which they termed A-cells (Fig. 2), and cells of a more fibroblastic appearance, the B-cells (Fig. 3). Cells of intermediate appearance were also present. The authors were uncertain whether these cells represented two distinct types or 'functional states manifested by a single type', a dilemma that has not yet been resolved. As will be seen in the next section, our own results support the latter interpretation.

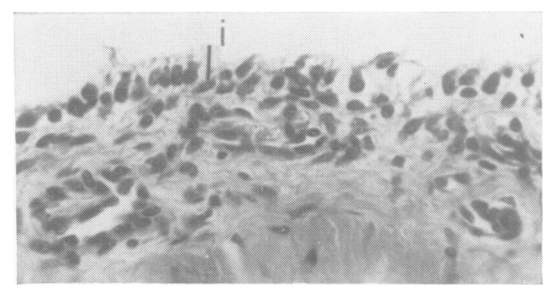

Fig. 1 *Section of synovium from metacarpophalangeal joint of normal pig. Note loose structure and branching cells of the intima (i) which rests on more compact, subintimal tissue. (Haematoxylin and chromotrope × 300)*

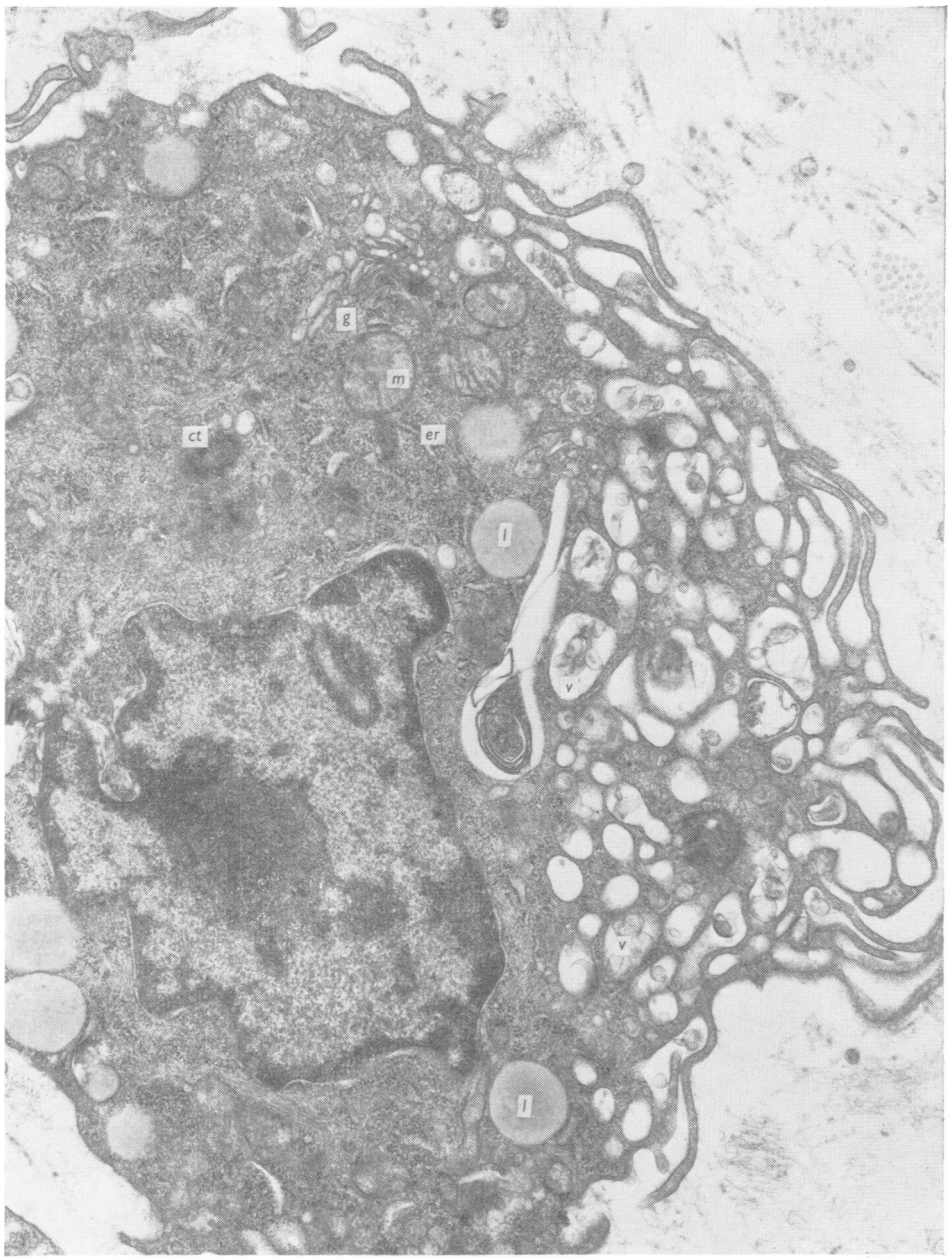

Fig. 2 *A-type cell typical of minority of cells in normal synovium. Note many fine lamellar extensions of the surface. Cytoplasm contains numerous large peripheral vacuoles* (v) *filled with granular and membranous material in addition to mitochondria* (m) *and lipid droplets* (l). *Golgi region* (g) *is extensive and contains a centriole* (ct). *Only a few cisternae of the endoplasmic reticulum* (er) *are visible* (× *23 000*). *Reproduced from Fell* et al., *1976, by kind permission of the Cambridge University Press.*

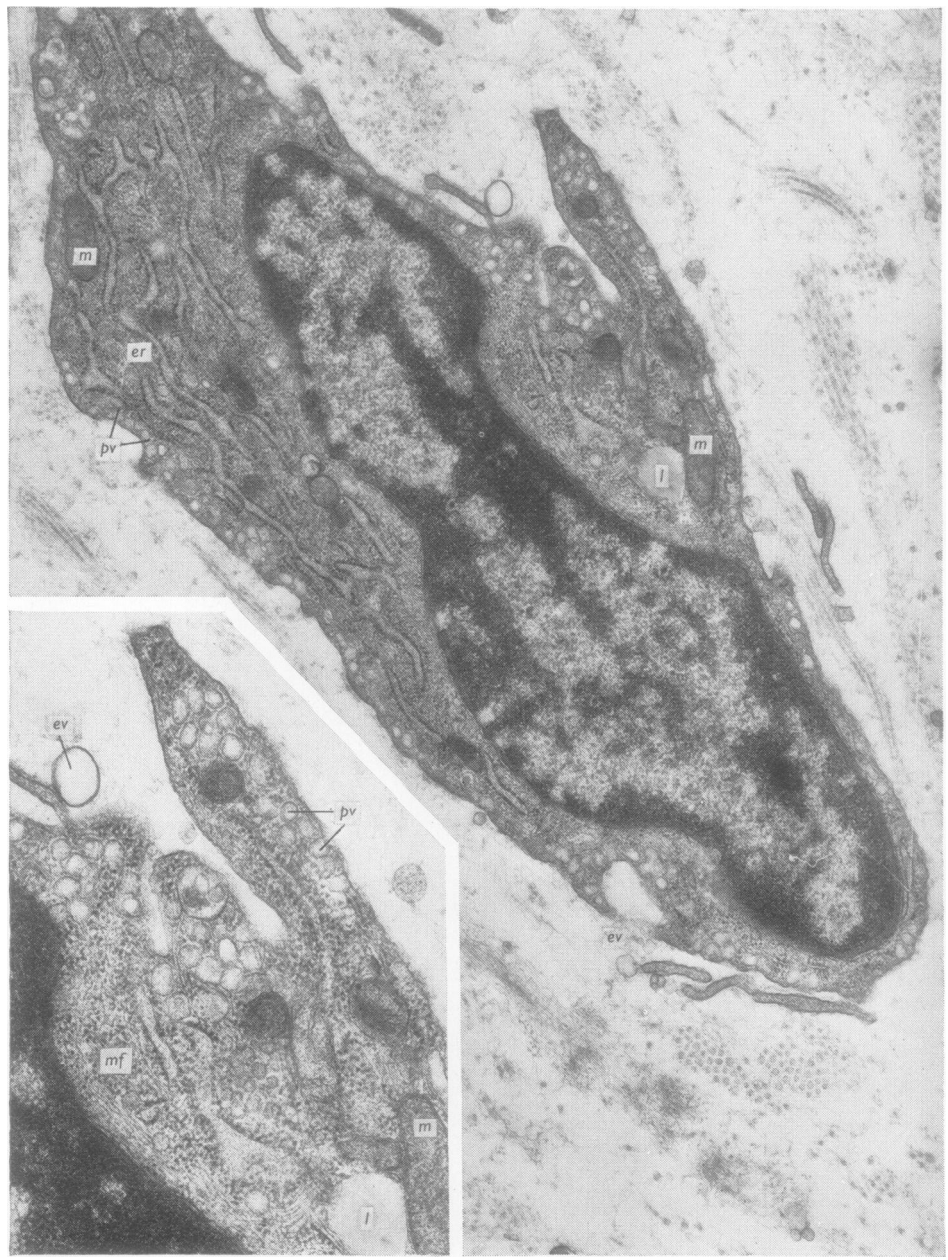

Fig. 3 *Thin section of B-type cell typical of most synoviocytes in normal intima. Note rows of small vesicles* (pv) *just inside plasma membrane. Cytoplasm contains cisternae of the rough endoplasmic reticulum* (er), *mitochondria* (m), *and arrays of microfilaments* (mf). *Extracellular vesicles* (ev) *are associated with the surface of the cell, 1, lipid droplet* (× *23 000. Inset* × *37 000*) *Reproduced from Fell* et al., *1976, by kind permission of the Cambridge University Press.*

The A- and B-cells are similar in appearance in the various species studied. Both types form long cytoplasmic branches which interweave with those of neighbouring cells. In addition the A-cells extend many lamelliform processes, which may correspond to undulating membranes, especially from the ends of their cytoplasmic branches. These processes, which are much less numerous in the B-cells, are usually termed 'filiform', but were they indeed filamentous they would not appear as continuous, usually curved profiles in thin section. The cytoplasm of the A-cells contains many vacuoles, a well-developed Golgi, but a very scanty rough endoplasmic reticulum. On the other hand, the B-cells have few vacuoles and a large rough endoplasmic reticulum. All that is certain about the functional activities of the two cell types is that the A-cells are much more phagocytic than the B-cells. The presence in the latter of a well-developed endoplasmic reticulum implies that they manufacture and secrete proteins of some sort, possibly enzymes. It has also been suggested that they secrete the hyaluronates of the synovial fluid, which are known to be produced by the synovium as a whole. But the respective functions of the A- and B-cells remain a matter for conjecture.

The relative proportion of A-cells to B-cells varies widely. Barland *et al.* (1962) report a minority of B-cells in human synoviocytes, Krey and Cohen (1973) found A-cells in the minority in the rabbit, and Fell *et al.* (1976) saw relatively few A-cells in the young pig. Whether this variation is correlated with species, age, the physiological state of the animal, or a combination of all three factors is not known.

The intimal cells are embedded in a matrix containing a loose network of fine fibres. In histological preparations this material looks very delicate, but manipulation shows it to be remarkably tough.

Histogenetic relationship of synoviocytes

We decided to investigate further whether the A-cells and B-cells of the intima are distinct types or merely different functional states of the same type. Two groups of experiments were made, one by means of organ culture (Fell *et al.*, 1976) and the other by short-term cell cultures (Barratt *et al.*, 1977).

ORGAN CULTURES

The principles of the method used are shown in Fig. 4. It will be seen that in the culture vessel isolated synovial villi were placed on a piece of millipore membrane so that on one side the intima of each villus was in contact with this substrate while on the opposite side it was covered only by a thin layer of fluid culture medium. After periods of incubation ranging from 24 hours to 10 days, the explants, still attached to the millipore, were fixed for histological examination by either electron or light microscopy.

After 4-6 days' cultivation, especially in thin villi (Fig. 5) the intimal cells on the upper, free surface differed sharply in appearance from those on the lower surface which were in contact with the millipore. The upper cells withdrew their long pseudopodia but retained their lamelliform processes and

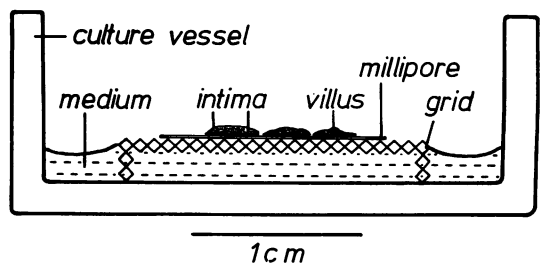

Fig. 4 *Diagram of isolated synovial villi in organ culture. Two flat-bottomed culture vessels (one shown) are enclosed in a Petri dish carpeted with filter paper soaked in isotonic NaCl to provide a moist chamber. Each vessel contains a shallow table of stainless steel mesh on which is placed a piece of millipore membrane (7μm pore size); 1·5 ml of fluid culture medium (the chemically defined medium BGJ5 + 15% normal heat-inactivated rabbit serum) is introduced into each vessel and replaced by fresh medium every 48 hours. Villi are snipped from the inner surface of a sheet of joint capsule and explanted on the millipore membrance. The Petri dishes with the culture vessels are enclosed in an air-tight pot (modified Fildes-Macintosh jar), gassed with an appropriate gas mixture, and incubated.*

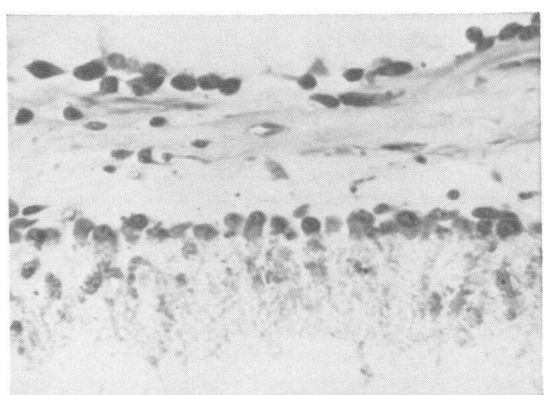

Fig. 5 *Section of villus after six days in organ culture. Intimal cells on upper surface resemble macrophages in rounded form, those on lower surface have extended long, richly branched pseudopodia deeply into the millipore membrane on which the explants rest. (Haematoxylin and chromotrope × 300)*

rounded up; in electron micrographs they were seen to have assumed the characteristics of A-cells, with a greatly reduced rough endoplasmic reticulum, well developed Golgi, and many cytoplasmic vacuoles and dense bodies. The intercellular material had largely disappeared and the cells seemed very lightly attached to the subintimal tissue.

The intimal cells on the lower surface of the villus in contact with the millipore membrane had the characteristics of B-cells. The cell bodies containing the nuclei were neatly aligned along the surface of the millipore, and each cell had protruded an intricately branched tassel of pseudopodia deep into the substance of the membrane. Electron microscopy showed a very large, sometimes almost hypertrophic, rough endoplasmic reticulum often with distended lumina filled with secretory material. Mitosis occurred on both sides of the explanted villi, but was much more abundant among the lower, branching cells.

The phagocytic activity of the intimal cells in the explanted villi was studied. A suspension of fine carbon particles was deposited on the surface of the synovium by injecting the material into the joint before dissection. In the explants the particles were avidly ingested by the A-type cells on the free surface of the villus, and many became stuffed with carbon. Some carbon-laden cells emerged from the intima and seemed about to drop off, but others became elongated and migrated downwards into the subintimal tussue. On the opposite side of the villus the highly branched cells next the millipore also ingested particles but much more slowly than the cells on the upper surface. As carbon accumulated in the cytoplasm the long branched processes were withdrawn, and the cells often reversed their orientation and migrated upwards into the subintimal tissue. These observations agree with those of Luckenbill and Cohen (1967), who injected a suspension of carbon into the knees of young chickens and noted the immediate uptake of particles by the intimal cells, even by those of the 'secretory type', and their subsequent transfer into deeper layers of the synovium. These authors suggest that 'avian synovial cells are capable themselves of removing carbon from the extracellular environment and carrying it to deeper layers'.

CULTURES IN SYKES-MOORE CHAMBERS

There are many papers on the behaviour of synovial cells in cell culture. The cultures, however, were maintained for weeks or months, by which time they consisted mainly of fibroblasts. We decided to examine the intimal cells in Sykes-Moore chambers (Sykes, 1973) (Fig. 6) during the first two days after isolation and before the overgrowth of fibroblasts had taken place. For a brief description of the chamber see Fig. 6.

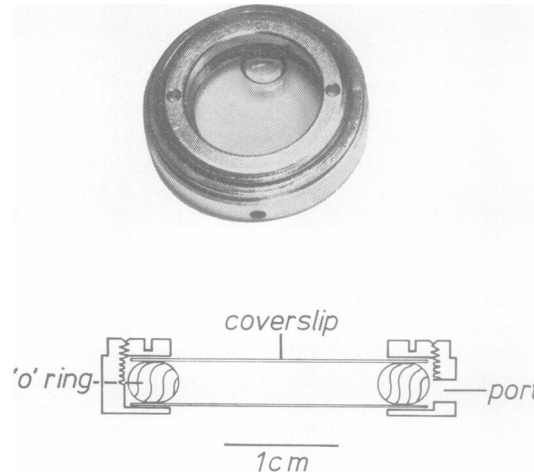

Fig. 6 *Photograph and diagram of Sykes-Moore chamber. The chamber consists of two coverslips separated by a rubber ring and screwed between the upper and lower parts of a metal casing. Ports have been bored through the metal through which the cell suspension, etc., may be injected. A large air bubble is left in the chamber to provide the cells with oxygen.*

To obtain the cells sheets of joint capsule were trypsinised enough to soften but not to disintegrate the tissue. Since the intercellular material of the intima is much less dense than the subintimal tissue the trypsin treatment made it possible to scrape off the intimal cells with a small knife and prepare a cell suspension which was then injected into a Sykes-Moore chamber (for details of the method see Barratt *et al.*, 1977). Although the normal synovial intima of the young pig contains only a small minority of A-cells, after 48 hours' incubation the suspension injected into the chamber had formed a sheet of cells of variable size (Fig. 7) which were indistinguishable in appearance from macrophages cultured under similar conditions. They did not divide. Scattered in this sheet were tiny colonies of typical fibroblasts usually emerging from fragments of small blood vessels; these provided useful internal controls for further experiments.

It was important to discover whether the macrophage-like cells in the chambers had physiological properties similar to those of ordinary macrophages. To investigate their phagocytic activity a suspension of carbon was added to the culture medium. The particles were rapidly and copiously ingested by the macrophage-like cells (Fig. 8) but very little was taken up by the tiny colonies of fibroblasts. Normal

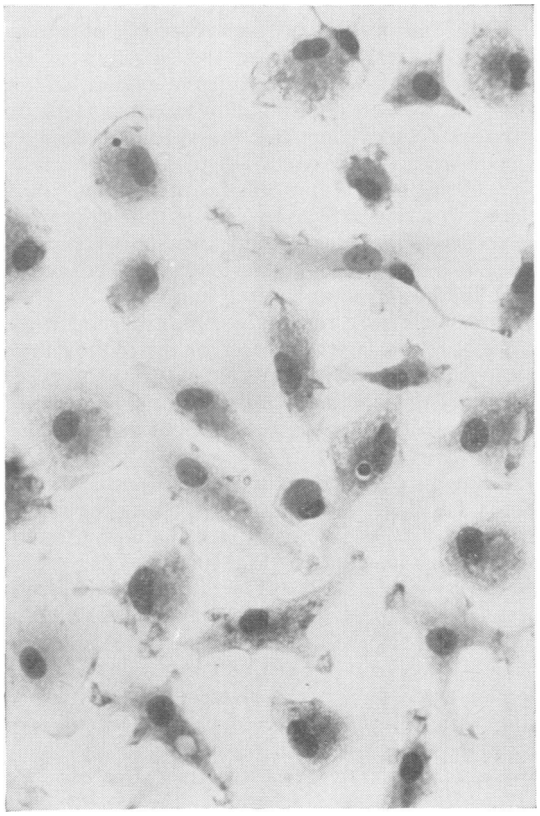

Fig. 7 *Intimal cells attached to floor of Sykes-Moore chamber after two days' incubation. Cells appear indistinguishable from normal macrophages cultured under similar conditions. (Haematoxylin alcoholic eosin × 400)*

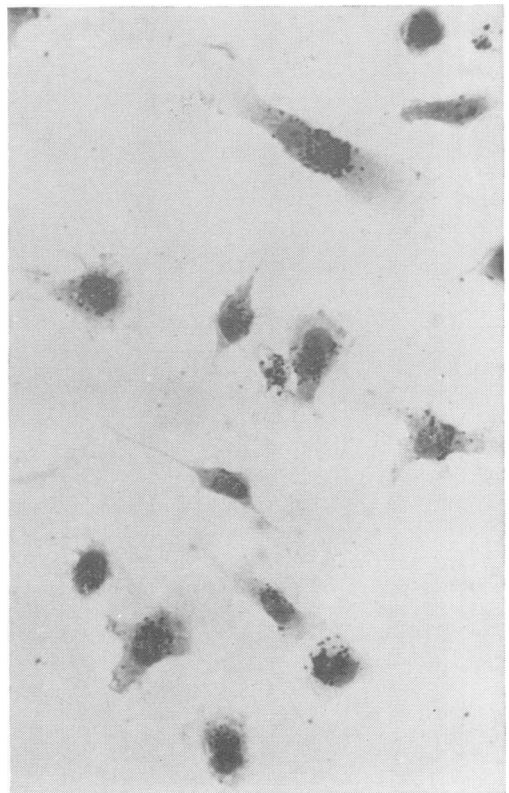

Fig. 8 *Intimal cells incubated for two days in a Sykes-Moore chamber in the presence of a suspension of carbon particles. Note that active phagocytosis has taken place. Fibroblasts in the same culture had few carbon grains. (Haematoxylin alcoholic eosin × 400)*

macrophages form antibody-opsonic rosettes when exposed to sensitised erythrocytes. To see whether the intimal cells in our cultures also had this property the chambers were incubated for 24-48 hours and sheep erythrocytes treated with rabbit antiserum against sheep erythrocytes were then introduced into the culture. Non-sensitised erythrocytes were added to the controls. After 30-60 minutes' incubation with the sensitised erythrocytes the cultures presented a remarkable appearance (Fig. 9). The macrophage-like cells were either thickly encrusted with sensitised erythrocytes (rosetted) or else, having ingested their rosette, they were stuffed with red cells in various stages of digestion. Fibroblasts in the same culture were not affected. In the controls a few cells had one or two erythrocytes stuck to the surface but the vast majority showed no adherence. There was no phagocytosis of red cells.

CONCLUSIONS

The results support the view (1) that the A-cells and B-cells of the synovial intima are different functional states of a single cell-type, and (2) that the intimal cells are closely related to normal macrophages.

Role of synoviocytes in breakdown of cartilage

As already mentioned, in inflammatory arthritis the synovium becomes heavily infiltrated with lymphocytes, plasma cells, and, in the early stages of the disease, neutrophil polymorphs. It is difficult therefore to know whether the synoviocytes themselves are concerned in the breakdown of the cartilage. Moreover, possibly the primary change is in the cartilage and its replacement by pannus is a secondary phenomenon (for a discussion of these questions see Gardner, 1972).

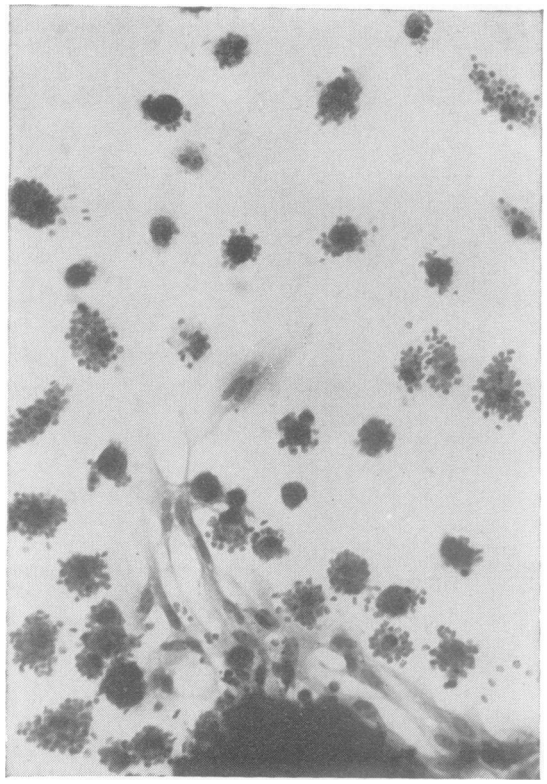

Fig. 9 *Similar culture after two days' incubation followed by 1 hour's exposure to sheep erythrocytes treated with antiserum to sheep erythrocytes. Intimal cells are encrusted with red cells (opsonic adherence) but fibroblasts in the same field are unaffected. (Haematoxylin alcoholic eosin × 250)*

That the synoviocytes were involved in the destruction of cartilage was first indicated by Hamerman *et al.* (1967), who observed some depletion of the matrix in cartilage explanted in a cell culture derived from a normal synovium (the effect was much greater when a culture of rheumatoid synovium was used). Recently the capacity of synovium from a normal joint to break down cartilage matrix *in vitro* has been investigated in organ culture by a method essentially the same as that shown in Fig. 4. Fell and Barratt (1973) found that when articular cartilage (pig) was grown for 10 days in association with a piece of synovium and subsynovial tissue the matrix lost metachromatic material near the site of contact with the synovial explant. This effect was greatly enhanced by the addition to the medium of complement-sufficient antiserum to pig erythrocytes.

These experiments have been extended by Fell and Jubb (1977). For this work we needed sets of equivalent synovial explants. Since the structure of the synovium varies widely in different regions of the same joint we were confronted by a serious technical problem. To overcome this the synovial villi were snipped from the inner surface of several sheets of joint capsule from a number of trotters; the villi were minced with fine iridectomy scissors; the mince was then pooled, washed, and centrifuged into a compact mass and a measured amount (0·025 ml) deposited on the millipore membrane in the culture vessel (Fig. 4) with a wide-bore pipette. In some experiments the fragment of cartilage was placed on top of the mince, in others the mince was deposited over one end of the explant. Controls were either paired pieces of isolated cartilage or explants in contact with dead (frozen-thawed) mince.

During 14 days' cultivation (Fig. 10a) the matrix of the cartilage in contact with living synovial tissue lost first its metachromatic material (proteoglycan), then its collagen (Fig. 10b), and in extreme cases disappeared altogether though the cells survived. This breakdown of the matrix was accompanied by cytological changes that were especially striking in the zone of cell columns and were well seen in explants partially overlapped by synovial mince (Fig. 11). There the chondrocytes became very basophilic, irregular in shape, and often multiplied by mitosis to form cell nests. Eventually they assumed a typical fibroblastic appearance. Control explants grown either in isolation or on dead (frozen-thawed) mince (Fig. 10c) did not show these effects.

To discover whether the chondrocytes played any part in the destruction of their matrix the experiments were repeated with dead (frozen-thawed) cartilage. When associated with living synovium the dead cartilage rapidly lost its proteoglycan (Fig. 10d) but the collagen (Fig. 10e) was much less actively degraded than in living cartilage taken from the same joint. Consequently the dead explants diminished in size more slowly than the living ones (compare paired explants, Figs. 10a, b, and c, d).

The fact that dead cartilage was degraded by living synovium implied that the synoviocytes had a direct, presumably enzymatic, action on the matrix. On the other hand, the observation that the living cartilage broke down more rapidly than the dead suggested that the chondrocytes also were concerned in the destructive process. To investigate this possibility cultures were prepared in which explants of living or dead cartilage were incubated in the same culture vessel as the synovial tissue but not in contact with it. In some experiments the two explants were placed on the same millipore but at a distance from each other, and in others the cartilage and synovium were explanted on separate millipores

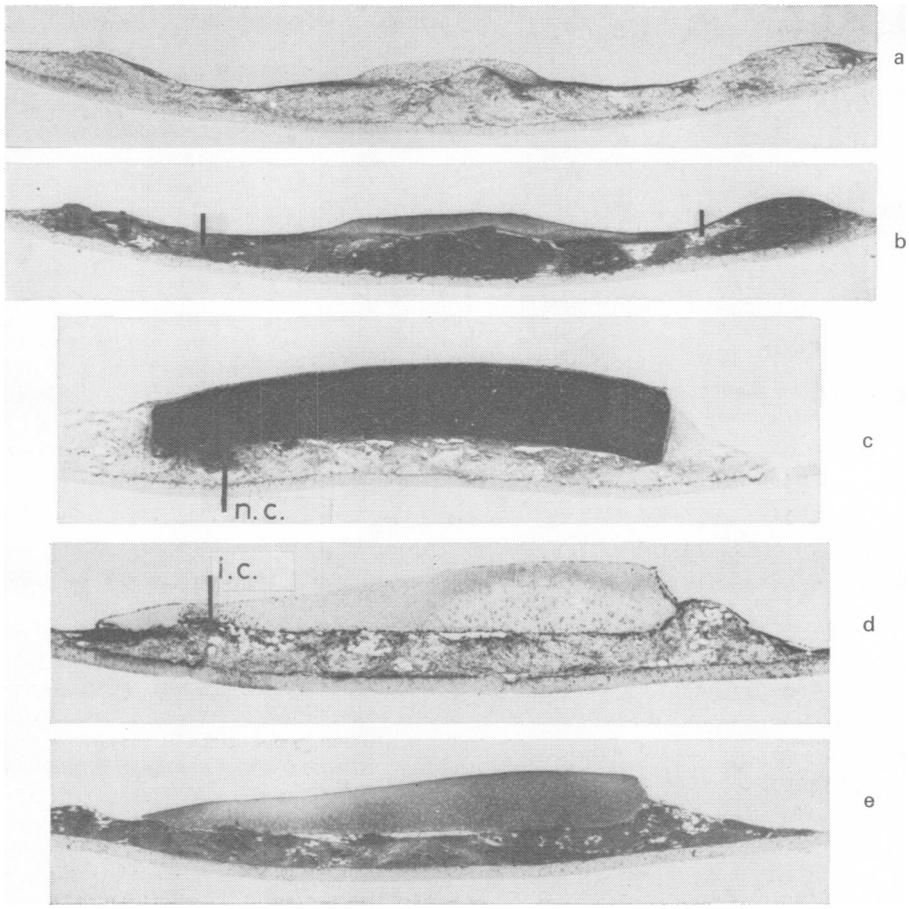

Fig. 10 *Living cartilage cultivated in organ culture for 14 days on top of a mass of living synovial mince;* (a) *Section stained with toluidine blue showing complete disappearance of metachromatic material (sulphated proteoglycan);* (b) *Section stained with celestine blue, Carazzi's haematoxylin, and van Gieson's stain showing degradation of the red-stained collagen. At either end of the explant the matrix has completely disappeared; its original length is shown by the vertical lines.* (c) *Living cartilage fixed after 14 days' cultivation on dead (frozen-thawed) synovium. The matrix is unaffected; cells have emigrated from the cartilage into the dead tissue where some have formed islets of new cartilage (n.c.) (toluidine blue).* (d) *Dead (frozen-thawed) cartilage incubated for 14 days on living synovium (paired explant to that seen in Fig. 10a, b). The metachromatic material has gone and synovial cells are invading the matrix (i.c.) (toluidine blue)* (e) *Section of same explant (celestine blue, Carazzi's haematoxylin, and van Gieson's stain) showing some degradation of the collagen but much less than in the corresponding living cartilage (Figs. 10a, b).* (× *16*)

resting on the same grid. Both systems gave the same results.

After 14 days' incubation under these conditions there was a conspicuous difference between the living (Fig. 12a, b) and dead (Fig. 12c, d) cartilage. Histological examination showed that the matrix of the living explant had lost both proteoglycan and collagen, though usually the extent of the depletion was less than that produced by direct contact with synovial tissue. The cells of the depleted region had undergone the same changes as those shown in Fig. 11. In contrast, the matrix of the dead cartilage appeared unaffected, and on biochemical analysis of the medium was found to have released no more

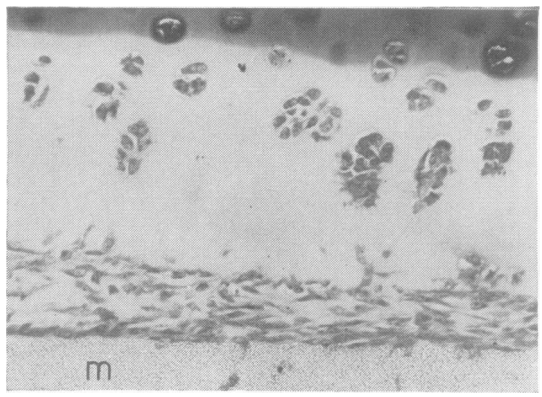

Fig. 11 *Cartilage partially overlapped by synovial mince and incubated for 10 days showing cytological changes in the chondrocytes in the area of the depletion. The cells become very basophilic, irregular in shape, and often divide by mitosis; some have wandered out of the cartilage and formed a layer of actively proliferating fibroblast-like cells between the millipore* (m) *and the cut surface of the explant (toluidine blue* × *170).*

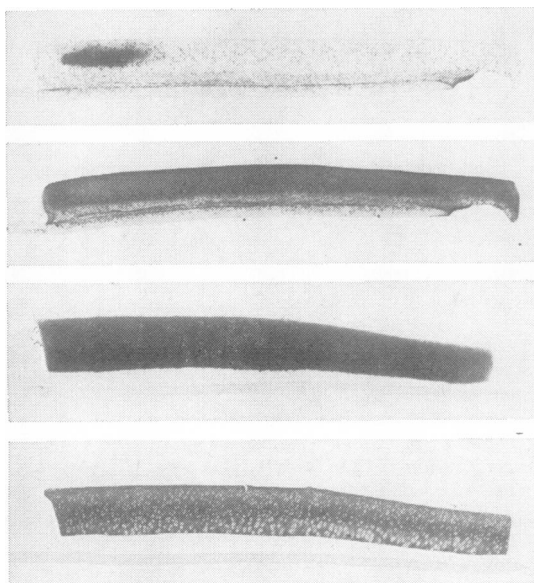

Fig. 12 *Paired explants from same strip of cartilage each incubated for 14 days on same piece of millipore as a synovial explant but widely separated from the synovial tissue.* (a) *Living cartilage showing loss of metachromasia (proteoglycan) from the matrix (toluidine blue).* (b) *Same explant; the collagen is severely depleted in the zone next the millipore (celestine blue, Carazzi's haematoxylin, and van Gieson's stain).* (c), (d) *Dead (frozen-thawed) cartilage; matrix appears unaffected by distant explant of synovial tissue* ((c) *toluidine blue* (d) *celestine blue, Carazzi's haematoxylin, and van Gieson's stain* × *16).*

proteoglycan than similar explants 'cultured' in isolation.

From these results it was clear that under the influence of the synovium the living chondrocytes were stimulated to digest their own matrix. Whether the synovium added or removed something from the medium to produce this effect is not known and is now being investigated.

CONCLUSION

In organ culture the synoviocytes cause the breakdown of cartilage by two mechanisms: (1) a direct, probably enzymatic action on the matrix, which requires contact between the two tissues and affects both living and dead cartilage; (2) an indirect action via the culture medium, which does not require contact between the tissues and affects only living cartilage.

Discussion

HISTOLOGICAL CLASSIFICATION OF INTIMAL CELLS

The question arises of how the intimal cells should be classified. As indicated above, there is strong evidence that the A-cells and B-cells first described by Barland *et al.* (1962) represent not two distinct cell types but different functional states of the same type and that the one form can change into the other in response to environmental factors. Since intimal cells in the A-form resemble macrophages in microscopic appearance, fine structure, phagocytic activity, and ability to form antibody-opsonic rosettes it seems appropriate to classify them as part of the 'mononucleate phagocyte system' (Langewoort *et al.*, 1970).

Should we then regard initimal cells in the A-form as ordinary macrophages and those in the B-form as clasmatocytes (the fixed macrophages of connective tissue), two forms known to be interchangeable, or as two types of highly specialised cells peculiar to the synovium? Henrikson and Cohen (1965) studied the development of the synovium in chick interphalangeal joints from the eighth day of embryonic life to the seventeenth day after hatching. A lining layer of cells, 'synovioblasts' differentiated which resembled those cells of the adult synovium that are intermediate in structure between the A- and B-forms (Barland *et al.*, 1962) rather than fibroblasts. Henrikson and Cohen, however, found no 'evidence for more than one cell type forming the synovial surface'. In the young pig (Fell *et al.*, 1976) relatively few A-cells were encountered in the normal synovial intima. Perhaps the differentiation into A- and B-cells increases with age, and hence the morphogenesis of the synovium should be studied in stages ranging

from birth to old age rather than in the fetus.

In experiments on phagocytosis *in vivo* (Luckenbill and Cohen, 1967) and in organ culture (Fell *et al.*, 1976) carbon-containing intimal cells were very mobile and migrated both into the subintimal tissue and on to the surface of the synovium, where they appeared to be on the point of dropping into the synovial fluid or (*in vitro*) into the culture medium. Cells poised on the surface of the synovium as if about to fall off were also often seen in the normal pig synovium (Fell *et al.*, 1976). These observations suggest that there may be a considerable turnover of intimal cells and their method of replacement—whether by mitosis of remaining cells or immigration of new cells via the blood vessels has not yet been ascertained.

Interpretation of the synovial intima depends on whether the A- and B-cells are derived from macrophages carried in the blood stream to the synovium, where they take up residence in the intima, or whether they differentiate *in situ*, which would imply that they are specialised cells peculiar to the synovium.

ROLE OF SYNOVIOCYTES IN BREAKDOWN OF ARTICULAR CARTILAGE

As described above, synovial tissue cultivated in organ culture in contact with either living or dead articular cartilage destroyed the matrix of the cartilage by a direct action. Since the synovial tissue was taken from normal joints any participation of inflammatory cells can be excluded, but as the synovial explants contained both intimal cells and fibroblasts we cannot tell which type of cell was responsible for the degradation or whether all the synoviocytes were involved.

Why synoviocytes of normal origin should have this severely destructive effect in our cultures is not clear, but it is thought to be a response to injury. In earlier experiments (Fell and Barratt, 1973) intact synovium with subsynovial tissue was much less injurious to cartilage than the more severely traumatised mince. Its effect was greatly enhanced, however, by the addition to the medium of complement-sufficient antiserum against pig erythrocytes which had virtually no effect on isolated cartilage. In the present experiments cell degeneration in the synovial explants was unlikely to be a factor, partly because there was surprisingly little necrosis even in the minced tissue, and partly because mince killed by freezing and thawing was ineffective.

It seems resonable to think that in inflammatory arthritis the synoviocytes probably have a direct action on the adjacent cartilage matrix similar to that observed in our organ culture experiments. On the other hand, it remains to be seen whether there is any phenomenon *in vivo* comparable to the indirect action on the matrix that *in vitro* the synoviocytes exert via the chondrocytes. How the indirect effect is produced is not yet known and is being investigated. Although the synovial mince releases proteolytic enzymes into the culture medium they are not in an active form, which no doubt explains why the matrix of dead cartilage appears unaffected when not in immediate contact with the synovial explant. Conceivably the synovial enzymes in the medium enter the cartilage and are then activated by the living chondrocytes. But more probably the chondrocytes are stimulated by some alteration in the medium to release enzymes that digest the surrounding matrix.

That the chondrocytes can degrade proteoglycan (Dingle *et al.*, 1975) and collagen (Fell and Jubb, unpublished) has been shown by experiments in which isolated cartilage was cultivated in the presence of vitamin A (retinol). Muirden *et al.* (1974) have presented evidence that in rheumatoid arthritis the chondrocytes participate in the destruction of their matrix. It would be interesting to know whether the synoviocytes induced this activity in the chondrocytes by an indirect mechanism comparable to that observed in our organ cultures. One final speculation: is it possible that in osteoarthrosis the change in the composition of the cartilage matrix that precedes its breakdown might also be due to an indirect action of the synoviocytes on the chondrocytes?

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