Living articular cartilage is not smooth

The structure of mammalian and avian joint surfaces demonstrated *in vivo* by immersion incident light microscopy

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William Hunter (1742–3) looked at the surface of articular cartilage ‘with a glass’. He found the surface ‘smooth,‡ polished, and covered with a membrane’. Hunter’s views were contained in a brief, classical paper in which he established the undisputed existence of the *circulus vasculosus* of the diarthrodial joint. On two of three counts it appears that he was mistaken, since the evidence contained in the present paper, and briefly reported on a previous occasion (Gardner and McGillivray, 1970), demonstrates that living articular cartilage is *not* smooth. Further, it has been accepted since the middle of the 19th century that the articulating surfaces are *not* covered by an extension of the synovial membrane, a view which prevailed as recently as 1838 (Bichat, 1801; Brodie, 1813; Henle, 1838) until proof of the absence of synovia from the cartilage surface was given by Leidy (1849); (Gardner and McGillivray, 1971).

Material and methods

The patellar, femoral condylar, and upper tibial surfaces of the knee joints of two adult male patients were observed during operation for uncomplicated meniscectomy. Observations were also made on fifteen female inbred albino Wistar (Edinburgh) rats, five Dunkin-Hartley guinea pigs, three TO female mice, two female New Zealand White rabbits, and five male and female broad-breasted bronze turkeys. The joints of three neonatal Wistar rats and of two living foetal TO mice were also investigated.

Polyvinylpyrrolidone (PVP) was selected as a synthetic synovial fluid substitute (Nuki, Ferguson, Boyle, and Boddy, 1969). PVP, at a concentration of 100 g./ml., has a relative viscosity at 37° of 187 centipoises and a refractive index of 1.43. As a clear viscous solution it offered the possibility of serving both as an immersion fluid for microscopy and as a synovial fluid substitute.

Joint surfaces were surveyed with a Zeiss operating microscope or with a Leitz Ortholux microscope fitted with X 6.5 and X 11 incident light objectives (Fig. 1). A perspex cone could be added to these objectives to permit

FIG. 1 *Leitz Ortholux microscope arranged for incident light microscopy. Illumination is provided by an internal, coaxial source or externally, by an oblique light source.*

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‡Most authors use the term smooth to mean ‘even, uniform, and not roughened in any way’ (Chambers’s Dictionary) [authors’ italics]; or (in accordance with the Concise Oxford Dictionary) to imply ‘freedom from perceptible projections or lumps or indentations or roughness’.

the lenses to be immersed in a fluid covering the joint surface. Coaxial tungsten filament illumination was provided and, as an alternative light source for photography, electronic flash. Additional, oblique, high intensity fibre optic and direct light sources were available. A Wild automatic camera, with interchangeable 6×8 cm. and 35 mm. heads, was used for recording surface appearances illuminated in these ways.

For *in vitro* studies, parts or the whole of freshly collected articular cartilage, with the associated underlying bone, were examined immediately or were plunged into cold buffered osmic acid. After fixation, the preparations were allowed to dry in air at room temperature. Some surfaces were mounted on plasticine and investigated without further treatment. Others were coated with a 10 nm. layer of a gold/palladium alloy after fixation and drying, as for scanning electron microscopy, and surveyed in this state.

To permit a comparison of air-dried and freeze-dried material, blocks of cartilage measuring not more than $2 \times 1 \times 0.5$ mm. were plunged into isopentane cooled to -70°C . with an alcohol/ CO_2 mixture and freeze-dried for 24 hrs at -60°C . and 0.01 tor, in a Pearse/Edwards tissue drier.

For *in vivo* studies, animals were anaesthetized with Nembutal (Pentobarbitone B. Vet. C) and placed either on a rectangle of cork on the mechanical stage of the microscope, or, in the case of larger animals, upon a makeshift operating table held in apposition to the microscope optical system. The knee joint was opened by a lateral incision in the axis of the limb. The joint was studied at once, the period of observation being recorded precisely. The articular surface was either exposed to air or covered with a solution of PVP. Under the latter circumstances, the perspex nose-cone fitted to the incident light objective was lowered into the PVP, establishing an immersion optical system. The PVP caused no recognizable change in the joint surface, prevented drying, and maintained viewing conditions intact for at least 1 to 2 hours. To investigate the effects of ischaemia, blood flow was halted by dividing the great vessels in the thorax without moving the joint from the field of observation.

Results

In vitro OBSERVATIONS (Fig. 2)

The surface of osmium-fixed and of freeze-dried articular cartilage from all animals is opaque. Freeze-dried preparations, however, permit a surface impression to be obtained of the red colour of underlying vascular channels. The location of these channels appears to coincide with the prominent margins of the $400 \mu\text{m}$. second order surface irregularities which are infrequent on rat but common on guinea-pig and turkey cartilages. In both air-dried and freeze-dried preparations the patterns of tertiary undulations are more easily seen, particularly when low-angle oblique incident light is used (Fig. 3, col. pl.), than when similar surfaces are studied *in vivo*. Dried preparations of acutely-angled articular surfaces can be rotated so that only a nar-

FIG. 2 Diagram representing the three orders of anatomical irregularity detectable *in vitro* and by the *in vivo* observation of living articular cartilaginous surfaces.

row zone remains in focus for photography. Under these conditions, the narrow line of focus records the gently undulating surface of the cartilage particularly clearly (Fig. 4, col. pl.).

In vivo OBSERVATIONS

Man

The cartilage surfaces of the first patient, aged 42, are found to be microscopically rough and it is concluded that the patient had developed early osteoarthritis, not detectable clinically. The surfaces of the knee of the second patient, aged 25, bear a pattern of shallow irregularities less orderly than the tertiary undulations described below on animal cartilages surfaces, and composed mainly of undulating prominences and intervening hollows resembling the secondary irregularities seen in young animals. In none of the zones examined is the cartilage smooth (Figs 5, 6, opposite).

Rat (Figs 7-12, col. pl.)

Immediately after opening a joint, the microscopic structure of the surface is difficult to distinguish due to a shiny, highly reflecting, and apparently wet surface covered with synovial fluid. Even at this stage an impression of underlying hollows is readily gained. In 1 to 5 min. the surface begins to appear more transparent and 6 min. after exposure the cartilage surface underlying the synovial fluid film is visible in its entirety.

FIG. 5 *Man: femoral condyle. Part of articular cartilaginous surface exposed at arthrotomy, of male aged 42. Note irregular surface pattern. Zeiss operating microscope. $\times 4$.*

FIG. 6 *Man: femoral condyle. Part of articular cartilaginous surface exposed at arthrotomy, of male aged 25. Compare irregular surface pattern with that shown in Fig. 5. Zeiss operating microscope. $\times 4$.*

The cartilage is transparent and surfaces perpendicular to the optical axis are not well seen; however, surfaces at an angle to the vertical light source can be seen and focused upon. The oblique light sources tested *in vivo* do not improve this view. There is a definite pattern of small tertiary undulations consistent with the appearance of the 20 to 40 μm . undulations recognized in the scanning electron microscope studies. The secondary undulations noted in the larger species described below are not prominent. Adjusting the focus allows the deeper layers of cartilage to be seen. Towards the edges are penetrating blood vessels; elsewhere the pattern suggests an end-on view of underlying trabeculae. No variation in this appearance is recognized on further observation for up to 1 hr after first exposure.

After the animal is killed there is no change in the appearance of the joint for 9 to 10 min. when barely visible surface undulations abruptly become white, one at a time, like a series of lights being turned on (Figs 13, 14). These changes are first seen over the femoral condyles and the lateral and medial borders of the patellar surface of the femur, but they later occur, to a lesser extent, in the patellar groove. They

continue to develop until 30 min. after death. Identical changes take place in a live animal observed in a moderately strong warm air current. In both situations many of the opacities disappear within 30 to 60 sec. of covering the surface either with saline or with PVP.

When PVP is used as a synovial fluid substitute and as an immersion fluid, the joint surface can immediately be seen microscopically without the temporary obscurity which occurs in the uncovered preparation. The pattern of hollows is similar to that seen in preparations exposed to the air *in vivo* except that the surface is less prominent, the cartilage slightly opaque, and the underlying vessels less readily apparent. Prolonged study of preparations covered with PVP reveals no noticeable change in the cartilage surface during a 60-min. period.

After the death of an animal, there is no immediate alteration in the surface appearance. After 5 min., however, the cartilage slowly becomes more transparent and vascular loops, previously obscure, slowly increase both in apparent number and in prominence.

In the neonatal rat, the total joint surface area is,

FIG. 3 Rat: femoral cartilage. Surface of femoral condyle, showing tertiary surface undulations. Material fixed in osmic acid and air-dried. Leitz incident light microscope. $\times 110$.

FIG. 4 Rat: femoral condyle. Margin of acutely-angled surface, with tertiary undulations seen at edge. Leitz incident light microscope. $\times 110$.

FIG. 7 Rat: lower end of femur. Patellar surface, exposed at arthrotomy but untouched. Secondary surface irregularities are clearly seen. Zeiss operating microscope. $\times 2$.

FIG. 8 Rat: femoral condyle. Articular surface of dead animal, for comparison with Figs 7, 9, and 10. Surface, not covered with PVP, was examined immediately after killing. Note tertiary undulations. Leitz incident light microscope. $\times 65$.

FIG. 9 Rat: femoral condyle. For comparison with Figs 7, 8, 10. Another area displaying pattern of tertiary surface undulations. Leitz incident light microscope. $\times 65$.

FIG. 10 Rat: femoral condyle. For comparison with Figs 8 and 9, fresh, freeze-dried specimen, showing pattern of tertiary surface undulations. Leitz incident light microscope. $\times 65$.

FIG. 11 Rat: femoral condyle. Vasculature of bone underlying articular cartilage, seen in intact, anaesthetized animal. Pattern of blood vessels corresponds to location of overlying secondary surface irregularities. Leitz incident light microscope. $\times 65$.

FIG. 12 Rat: femoral condyle. Effects of ischaemia are shown. Circulation to joint has been cut off. Vessels in

underlying bone are prominent and congested. Leitz incident light microscope. $\times 65$.

FIG. 13 Rat: femoral condyle. Effects of drying 15 min. after onset of ischaemia. Small, white, refractile surface foci have begun to appear. Compare with Fig. 14. Size of opaque foci approximates to that of tertiary surface undulations. Leitz incident light microscope. $\times 65$.

FIG. 14 Rat: femoral condyle. Compare with Fig. 13. In this photograph the surface appearances after 30 min. of ischaemia are shown. Leitz incident light microscope. $\times 65$.

FIG. 15 Mouse: condylar surface of femur. Surface is viewed through PVP during life. Both secondary irregularities and tertiary undulations can be identified. Leitz incident light microscope. $\times 65$.

FIG. 16 Mouse: femoral condyle. Dried specimen, after fixation in osmic acid, for comparison with Figs 15 and 17. Leitz incident light microscope. $\times 65$.

FIG. 17 Foetal mouse: femoral surface. Compare with Figs 15 and 16. The customary pattern of tertiary undulations is shown on the patellar surface of the femur. Leitz incident light microscope. $\times 65$.

FIG. 18 Turkey: tibial condyle. At margin of tibia, a coarse pattern of surface irregularities is seen. Dry specimen, fixed in osmic acid. Leitz incident light microscope. $\times 65$.

FIG. 19 Turkey: tibial condylar surface. Coarse pattern of secondary surface irregularities and of shallow surface tertiary undulations bears conspicuous, superimposed fibre pattern. Dry specimen, fixed in osmic acid. Leitz incident light microscope. $\times 65$.

of course, smaller than in the adult animal. Nevertheless, an identical pattern of (smaller) surface hollows is seen.

Mouse (Figs 15, 16, 17)

The articular surfaces are qualitatively similar to those of the rat. In air they are at first covered by an obscuring fluid which then clears to reveal undulations resembling those seen in the rat, and, in spite of the smaller surface area of the joint, of about the same size. This pattern is also observed in foetal mice. Mouse joint surfaces immersed in PVP show the same hollows and do not change in pattern within 30 min. of observation in the live animal.

Guinea-pig

The surface structure of guinea-pig articular cartilage is essentially the same as in the rat although slight differences are noted on close observation. In addition to the small 20 to 40 μm . undulations, there are larger irregularities, particularly towards the lateral and, to a lesser extent, towards the medial side of the patellar surface of the femur. These

larger irregularities frequently seem to form a honeycomb type of arrangement containing, in each division so formed, a large number of the small undulations. The impression is gained that the ridges bounding these areas might lie above blood vessels; this view is substantiated when, after death, a vascular pattern of this kind appears beneath the ridges of a surface preparation covered with PVP.

Rabbit

Immobilization of the rabbit below the microscope objectives was difficult and rabbit joints were only observed while the animal was held in the hand. In spite of this difficulty, which impaired photography, an identical pattern of small surface hollows was recognized on the articular cartilages.

Turkey (Figs 18, 19)

There are several differences between the surface structure of turkey cartilage and that of mammals. The shape of the distal end of the femur is different and there is a deeper and longer inter-condylar groove. However, the surface shows a pattern of small 20 to 40 μm . hollows similar to that in the rat.

To face p.6. This plate should be viewed in tungsten light, not daylight.

A network of blood vessels passes through the cartilage, and the vessels are more numerous than those seen in the guinea-pig. These vessels are not found beneath the surface of the cartilage of the intercondylar groove but appear, and become progressively more numerous, towards the outer margins of the medial or lateral condyles. A pattern of irregularities in the transparent cartilage deep to these vessels similar to the cartilage surface pattern seen superficial to them suggests that the vessels penetrate the cartilage rather than simply lying beneath the cartilage surface. Surface drying reveals ridges formed over many of these vessels.

The surfaces of turkey cartilage do not show a pattern of second order irregularities but, instead, display a pattern of longitudinal and cross-bands, of about the same diameter, with their surfaces overlaid by 20 to 40 μm . tertiary undulations. Longitudinal bands are most prominent on either side of the patellar groove; cross-bands are noted traversing the intercondylar notch inferiorly and posteriorly, becoming barely visible within the groove but remaining prominent at the sides. In some areas there is intermingling of the two orientations of ridges. Careful observation often reveals parallel bands ranging in colour from grey to white, suggesting the presence of bundles of material, possibly collagen. These bands give an impression of more depth to the surface ridges than is suggested by differences in depth of focus between high and low points on the surface.

PVP is physically difficult to apply to the joint surfaces of the turkey, because of the acutely rounded contours of the condyles. Observations with PVP show, nevertheless, the same immediate *in vivo* findings as in mammals but there is no tendency for the underlying trabecular and vascular pattern to increase in prominence after death. Fixed and freeze-dried specimens display identical features.

Discussion

The experiments described in this paper have shown conclusively, and for the first time, that articular cartilage *in living mammals and birds*, has a characteristic surface pattern of small, orderly, shallow hollows and prominences. The present observations have established that the surface irregularities first recognized by scanning electron microscopy are real and that they are not caused by autolysis, fixation, drying, metallic coating, high vacuum, electron bombardment, or any of the preparative steps used by those authors who have described these patterns either in scanning electron microscopic or incident light investigations of dry tissue *in vitro*. The preliminary studies reported in this paper of the cartilaginous surfaces of the knees of two adult human males suggest strongly that human articular

surfaces, also, are not smooth. These observations remain to be extended and confirmed in younger adults and in children in whom any question of coincident disease can be excluded.

The impression conveyed by human articular surfaces seen at surgical operation and covered by thin films of synovial fluid, is of remarkable smoothness and, until recently, there has been practically no criticism in the literature to dispel this impression. A short historical review of the development of knowledge of normal joint surfaces is given in the subsequent paper (Gardner and McGillivray, 1971). However, the introduction to medical research of scanning electron microscopy has thrown doubt on the classical view that articular cartilage is smooth, revealing, on dry mammalian cartilage surfaces, broad undulations of about 400 μm . diameter, together with finer 20 to 30 μm . hollows (Gardner and Woodward, 1969; Inoue, Kodama and Fujita, 1969; Walker, Sikorski, Dowson, Longfield, Wright and Buckley, 1969) superimposed on the larger undulations. It has been found that the broad 0.5 mm. undulations can be seen with a simple hand lens. The smaller hollows are only detectable under advantageous optical conditions, using incident light at a low angle and a good quality stereoscopic dissecting microscope, or with an incident light microscope (Gardner and Woodward, 1969). There seems little doubt, therefore, that the irregularities shown by scanning electron microscopy are real.

The investigations of joint surfaces by scanning electron microscopy have nevertheless been criticized on physical and on biological grounds. Preparations for scanning electron microscopy must be dry since they are viewed under high vacuum. Material from joint surfaces has been fixed therefore in cold osmium tetroxide (Gardner and Woodward, 1969) or formalin (Inoue and others, 1969) immediately after removal from the body, and allowed to dry in air; alternatively, the material has been freeze-dried (Walker and others, 1969). The dry material is then invariably coated with a thin, electrically conductive metal such as a gold/palladium alloy to prevent surface charging during scanning. Each of these preparative steps can presumably introduce artefacts. Biologically, the material scanned is necessarily inert, has been deprived of a blood supply for varying periods before fixation or freeze-drying, and may even have been allowed to undergo preliminary drying and autolysis. The justification for accepting this pathological tissue for analysis has generally been the assumption that because normal cartilage is 'avascular', changes in surface structure are unlikely to be rapid.

The technical limitations imposed by these possible physical and biological artefacts have

restricted interpretation of scanning electron micrographs or of the photographs taken by incident light microscopy, either of fresh or of fixed tissue *in vitro*. To overcome these objections and to avoid drying, distortion, autolysis, and fixation, it was necessary to devise an additional experimental approach that would permit the *in vivo* observation of intact articular cartilage surfaces. These were the reasons underlying the introduction of the technique described in the present paper. With this new approach it has been demonstrated that living cartilaginous joint surfaces are not smooth, that the scanning electron microscopic investigations showing surface irregularities are valid, and that articular cartilage alters in physical characteristics within 15 min. of the onset of ischaemia.

In many of our animal experiments it was difficult to tell whether the surface irregularities observed were primarily a pattern of hollows or of prominences. Nor did photography help, since an illusion of pits or mounds could be created by reversing the transparency and varied, with visual accommodation, from minute to minute. Scanning electron microscope evidence at first suggested that the primary pattern was one of hollows but this may be incorrect, as other evidence, including the appearance of cryostat and paraffin sections of cartilage, suggests that these irregularities may represent the protrusion of flattened superficial chondrocytes above the plane of the cartilage surface. Clarke (personal communication) has adduced evidence to suggest that at least some of the indentations seen by the scanning electron microscope represent collapsed chondrocytes.

We have shown that differences exist in the pattern of secondary surface irregularities in the five mammalian species studied and in the turkey. The pattern of minute tertiary surface undulations was remarkably constant from species to species. Similar but smaller undulations were present on foetal cartilage surfaces and there is no evidence that the formation of surface undulations is induced by mechanical movement or loading.

The use of PVP as an immersion fluid was valuable in studying *post mortem* changes, as it prevented surface drying, a process which would have obscured other alterations in the cartilage. Death could be confirmed by direct observation of synovial vessels. The increased prominence of blood vessels beneath cartilage that followed cessation of blood flow is not readily explained. It may represent venous stagnation or, alternatively, a rapid change in cartilage translucency caused by fluid shifts associated with ischaemic interruption to the normal passage of extracellular fluid through cartilage matrix.

The changes observed when freshly exposed mammalian, animal cartilage surfaces were allowed

to dry, or when the blood supply to the living joint was interrupted, were particularly interesting. The highly reflecting liquid surface film, which disappeared soon after the exposure of a cartilage surface at arthrotomy, was probably synovial fluid. The apparent increase in cartilage transparency occurring at this time probably represented reduced light diffraction rather than drying. The same effect was achieved by immersing the objective lens in a fluid, coating the surface. The rapidity with which the initial fluid coating dried suggested that drying artefact would occur rapidly if steps to prevent it were not taken. It was remarkable, however, that unless exceptional drying conditions existed, such as in a warm room or in an air current, the exposed joint surface remained moist as long as the animal remained alive. Drying, manifested by the development of multiple minute refractile surface opacities equal in size to the area of tertiary surface undulations, occurred rapidly after death. This is likely to be due both to decreased perfusion pressure through cartilage and to the decreased permeability demonstrated, in cartilage, within 10 min. of death (Brower, Akahoshi, and Orlic, 1962). This finding might suggest that, in addition to the well-established role of synovial fluid in cartilage nutrition, perfusion of cartilage from underlying vessels also plays a role in cartilage metabolism.

The extraordinary observation of a sequential development at a constant time after death of minute, refractile surface opacities approximately equal in size to the area of a surface hollow or prominence, suggested the possibility that there are early ischaemic changes in chondrocyte fluid content. It appeared possible that the sudden appearance of clusters of opaque surface islands could be accounted for by the sudden ischaemic assimilation of fluid by chondrocytes. If evidence to support this view could be obtained, it would throw doubt on the validity of surface structural studies or of mechanical characteristics and lubrication properties, made with cartilage which had been deprived of arterial blood supply for more than 15 min. Were this view to be sustained by direct evidence of a rapid ischaemic change of cartilage cell and matrix structure, then there would exist some reason for questioning measurements of lubrication, mechanical strength, and biochemical composition made with *post mortem* material. A reappraisal of the problem of joint lubrication, no less radical than that which has been provoked by proof of the undulating character of articular cartilage surfaces, would then be desirable.

Summary

Cartilaginous joint surfaces in *living* normal humans, rats, mice, rabbits, guinea-pigs, and turkeys were examined by incident light microscopy. Polyvinyl-

pyrrolidone was used as an immersion fluid to cover the animal joint surfaces during some of these observations. The results of these *in vivo* experiments were contrasted with those obtained from the investigation of fresh rat cartilage *in vitro* and with earlier studies of articular surfaces made with the scanning electron microscope.

It was shown first, that foetal and adult mammalian articular cartilage surfaces bear, during life, a series of very shallow undulations, approximately 20 to 30 μm . in diameter. A similar pattern of undulations was recognized on the surface of avian (turkey) cartilage. Limited studies of living human cartilage suggested that the pattern of surface irregularities in adult man is less orderly.

It was further shown that changes in the appearance of animal cartilage surfaces, attributable to drying, began 10 to 15 min. after blood flow to the joint ceased but very much more slowly in the living joint. These drying effects could be prevented by covering the observed surfaces with polyvinylpyrrolidone, a synthetic synovial fluid substitute.

The present results confirm earlier observations, made *in vacuo* with the scanning electron microscope, that normal articular surfaces are not smooth.

Theories of joint lubrication must now take account of the presence of this ubiquitous surface structure and laboratory studies of the mechanical properties of cartilage must consider the rapid surface changes which result from ischaemia, death, or drying.

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