

## The interrelationship of cell density and cartilage thickness in mammalian articular cartilage

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Estimation of the cellularity of articular cartilage has usually been undertaken as a subsidiary part of investigation of the tissue metabolism. Consequently the choice of species or joint has been influenced by availability or convenience for biochemical analysis. Information has been obtained for rabbit (Bywaters, 1937; Barnett, Cochran & Palfrey, 1963; Mankin & Baron, 1965) and human femoral condylar cartilage (Stockwell, 1967); human patellar and humeral head cartilage (Meachim & Collins, 1962); horse carpal (Bywaters, 1937) and bovine metacarpo- and metatarsophalangeal joints (Rosenthal, Bowie & Wagoner, 1941). In general it may be deduced that cartilage from smaller species is more cellular than that from larger species, and that the cartilage in small joints of large animals resembles that in large joints of small animals (Barnett, 1963). However, in the studies cited there are insufficient features in common, either in the techniques employed or in the species or type of joint investigated, to enable much useful comparison.

The present study attempts to provide more systematic data for a number of species and different joints. It is shown that there is an inverse relationship between cell density and the thickness of articular cartilage. The findings are relevant to the nutrition and to some aspects of the growth and pathology of the tissue.

### MATERIAL AND METHODS

Articular cartilage was obtained from young adult specimens of the following species: mouse, rat, cat, rabbit, dog, sheep, cow and man. In each species femoral condylar cartilage was examined; other joints were also sampled. In man these included the shoulder (humeral head), the ankle (trochlear surface of talus), the metatarsophalangeal joints (metatarsal surface), the interphalangeal joints (proximal surface) and the incudomalleolar and incudostapedial joints. Human specimens were obtained either post-operatively or post-mortem. Altogether 66 joints were investigated.

From the larger joints, a block of the full depth of the cartilage (including a small part of the subchondral bone) was fixed in 10 % neutral formalin, passed to wax, and cut at 10  $\mu$ m normal to the articular surface. In the case of small joints, a considerable part of the long bone bearing its articular cartilage was decalcified in formic-citrate (Pearse, 1968), after formalin fixation, before subsequent embedding and sectioning as above. Sections were stained with haematoxylin and eosin.

*Cell-counting procedure*

Nuclear counts were made using a squared graticule and magnifications of either  $\times 100$  or  $\times 400$  approximately. The number of nuclei or parts of nuclei which lay in a rectangular area with its long side parallel to and abutting on the articular surface was recorded. This was repeated in similar rectangular areas, successively more distant from the articular surface and with their long sides adjacent, until the junction of the basal calcified cartilage with the rest of the cartilage was reached. In this way the full thickness of the uncalcified portion of the articular cartilage was examined. This was repeated until in each specimen of thick cartilage up to 1000 nuclei, and in each specimen of thin cartilage 200–300 nuclei, had been counted. Several sections from each specimen were examined. Thus 'crude' estimates of the cell density (cells per  $\text{mm}^3$ ) could be calculated for the whole depth of the uncalcified portion of the cartilage.

Since the same nucleus can appear in more than one successive histological section, a correction (Abercrombie, 1946) must be made to the 'crude' cell density (C) involving both the section thickness (S) and the diameter of the nucleus (N). The corrected cell density =  $C[S/(S+N)]$ . This is an estimate of the number of cells per  $\text{mm}^3$  of fixed tissue on the slide. It is difficult to ascertain the section thickness precisely. It was measured rather inexactly by focusing the oil immersion objective lens ( $\times 100$ ) on the top and bottom of the section; the distance moved by the microscope stage was multiplied by the refractive index of the mounting medium. For each section the results of this manoeuvre were quite variable, although they indicated that the nominal thickness given by the setting on the microtome was acceptable as a basis for calculation.

Nuclear diameters were measured in the same sections as those used for the nuclear counts, but using a stepped graticule and a magnification of  $\times 1000$ . Following the procedure of Rosenthal *et al.* (1941) the maximum and minimum diameters of about 100 nuclei were measured. These were distributed throughout the full depth of the articular cartilage. The mean nuclear diameter was calculated as the diameter of the sphere equivalent in volume to that of the chondrocyte nucleus (regarded as a regular ovoid).

Articular cartilage thickness was measured in the sections from the articular surface to the junction of the uncalcified with the basal calcified zone. A number of measurements were made in each specimen, corresponding to the regions of the sections where nuclear counts were made.

## RESULTS

The thickness of femoral condylar cartilage varies widely from species to species and ranges from about 0.05 mm in the mouse to about 2.3 mm in man (Table 1). It is proportional to the body weight of the species (Fig. 1), the relationship being of the simple allometric type, but the thickness of human cartilage is more than would be required in order to fit the relationship. Articular cartilage from sites other than the knee joint is also extremely variable in thickness (Table 2). In small human joints, the thickness can be much less than that observed in the knee joint, that of the human incudomalleolar joint being less than that of the mouse femoral condyle.

Cell density diminishes with increasing distance from the articular surface (Fig. 2), although it tends to fall to a constant level in the deeper parts of the tissue. Thus, where joints of different sizes are involved, it is difficult to compare a stratum of tissue at a given depth in the articular cartilage. It is most useful to compare the specimens on the basis of the cell density of the whole thickness of the tissue. The

Table 1. *Cell content and related data for femoral condylar cartilage*

(Although there is a large variation in the body weights of the dogs, the cartilage thickness of the individual specimens conforms to the relationship to body weight found for the mean values of the different species.)

Species (no. of specimens)	Body weight (kg)	Cartilage thickness (mm)	Corrected cell density (cells $\times 10^{-3}/\text{mm}^3$ )	No. of cells ( $\times 10^{-3}$ ) deep to 1 mm <sup>2</sup> articular surface
Man (7)	72 $\pm$ 9.5*	2.26 $\pm$ 0.49	14.1 $\pm$ 3.2	31.0 $\pm$ 4.8
Cow (3)	c. 600	1.68 $\pm$ 0.12	19.8 $\pm$ 4.1	32.9 $\pm$ 4.7
Sheep (3)	50 $\pm$ 5.5	0.84 $\pm$ 0.26	52.9 $\pm$ 12.6	42.3 $\pm$ 6.0
Dog (7)	23.7 $\pm$ 11.9	0.67 $\pm$ 0.28	44.4 $\pm$ 11.6	27.2 $\pm$ 8.4
Rabbit (6)	3.2 $\pm$ 0.71	0.214 $\pm$ 0.067	188 $\pm$ 56	37.3 $\pm$ 5.5
Cat (4)	2.3 $\pm$ 0.26	0.327 $\pm$ 0.150	108 $\pm$ 33	32.1 $\pm$ 4.4
Rat (4)	0.28 $\pm$ 0.04	0.072 $\pm$ 0.013	265 $\pm$ 57	18.6 $\pm$ 2.7
Mouse (4)	0.025 $\pm$ 0.004	0.058 $\pm$ 0.007	334 $\pm$ 41	19.4 $\pm$ 1.6

\* Means  $\pm$  1 standard deviation.

Table 2. *Cell content and related data for articular cartilage other than from the femoral condyles*

Species	Source of cartilage (no. of specimens)	Cartilage thickness (mm)	Corrected cell density (cells $\times 10^{-3}/\text{mm}^3$ )	No. of cells ( $\times 10^{-3}$ ) deep to 1 mm <sup>2</sup> articular surface
Man	Humeral head (2)	1.56, 1.32	16.8, 12.4	26.2, 16.4
	Talus (2)	2.16, 1.44	11.4, 12.9	24.8, 18.6
	Metatarsal (2)	1.50, 1.02	13.7, 18.6	20.6, 19.0
	Phalanges (4)	0.87 $\pm$ 0.19	20.7 $\pm$ 2.1	17.3 $\pm$ 2.7
	Incudomalleolar, incudostapedial joints (5)	0.032 $\pm$ 0.005	595 $\pm$ 109	19.5 $\pm$ 6.4
Dog	Humeral head (4)	0.68 $\pm$ 0.12	38.5 $\pm$ 11.9	25.2 $\pm$ 4.7
Cat	Metatarsal (3)	0.138 $\pm$ 0.037	146 $\pm$ 12.8	20.1 $\pm$ 5.7
Rat	Humeral head (2)	0.128, 0.165	116, 121	14.9, 20.0
	Metatarsal (1)	0.083	233	19.3
Mouse	Humeral head (3)	0.055 $\pm$ 0.010	329 $\pm$ 38	18.1 $\pm$ 2.2

corrected values for cell density of the femoral condylar cartilage are given in Table 1. As with cartilage thickness, there is a considerable variation between the species. A 24-fold difference is observed between mouse (330 000/mm<sup>3</sup> approximately) and human cartilage (14 000/mm<sup>3</sup>). The cell density appears to vary inversely with the body weight of the species and also, therefore, with the cartilage thickness. Different joints of species of different size may have articular cartilage with the same

cell density. This is the case with rat humeral head and cat metatarsal cartilage (Table 2). In this example, cartilage thickness is about the same in the two specimens (Fig. 3), although there is a ten-fold difference in the body weights of the two species. A second example, where there is a more marked difference in the body weight, is that of mouse femoral condylar cartilage and the human incudomalleolar joint (Tables 1, 2; Fig. 4).

The relationship between cell density and cartilage thickness is very similar, either for the same joint in different species, or for different joints in the same species. Thus,

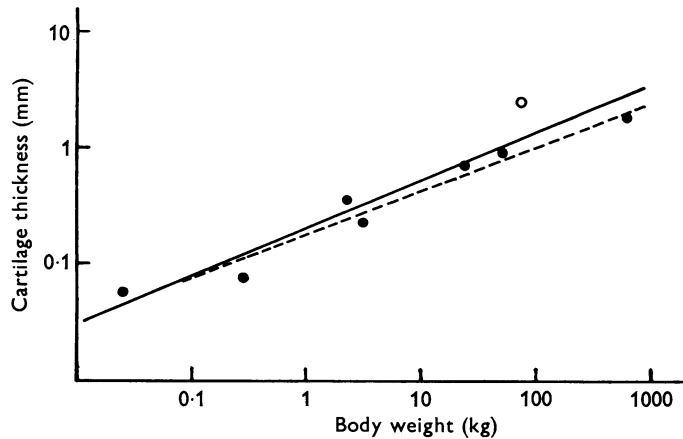


Fig. 1. Relationship of thickness of femoral condylar cartilage to body weight. All species: ●—●,  $y = 0.189x^{0.40}$ . Excluding man (○): ●—●,  $y = 0.176x^{0.37}$ .

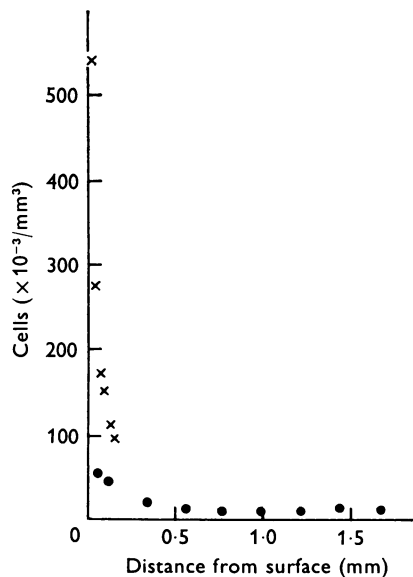


Fig. 2. Variation of cell density with distance from the articular surface. Rabbit (x) and human (●) femoral condylar cartilage.

for femoral condylar cartilage, the relationship between the species is given by  $y = 32000x^{-0.88}$ , where  $y$  = cells per  $\text{mm}^3$  and  $x$  = cartilage thickness in mm. For all human joints studied,  $y = 23200x^{-0.91}$ . Hence, when different joints in the same species are considered, cell density appears to be a function of cartilage thickness rather than body weight. The inverse relationship is shown in Fig. 5 for all joints investigated, the calculated regression line corresponding to  $y = 27900x^{-0.88}$ . It must be stressed that wide variations occur around the general relationships expressed by these formulae.

These relationships, although not quite linear, indicate that the total number of chondrocytes deep to a unit area of articular surface should be about the same in all

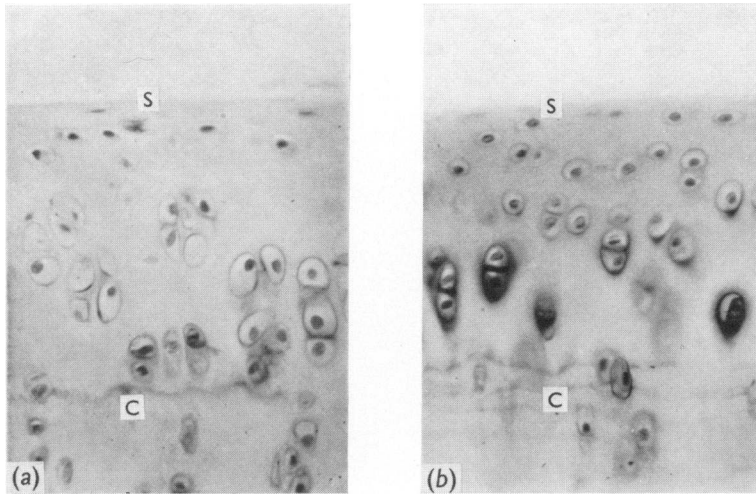


Fig. 3. (a) Rat articular cartilage, humeral head. (b) Cat articular cartilage, metatarsal head. S = articular surface. C = calcified zone. Haematoxylin and eosin.  $\times 300$ .

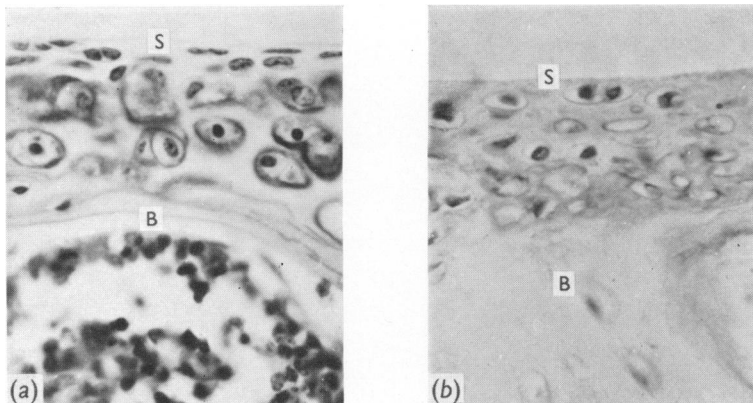


Fig. 4. (a) Mouse articular cartilage, femoral condyle. In the region shown, the calcified zone and subchondral bone plate are extremely thin. (b) Human articular cartilage, malleus. S = articular surface. B = subchondral bone. Haematoxylin and eosin.  $\times 480$ .

joints and species. This is true within rather wide limits (Tables 1, 2); for all specimens studied it is found that there are  $25\,500 \pm 8800$  cells deep to  $1\text{ mm}^2$  of articular surface. This absolute cell number (as distinct from the cell density) is consistently larger in thicker cartilage: for example, human femoral condylar cartilage contains 31 000 cells deep to  $1\text{ mm}^2$  while in rat and mouse cartilage the cell number is reduced to about 19 000. Nevertheless, the values for the cell number are remarkably close.

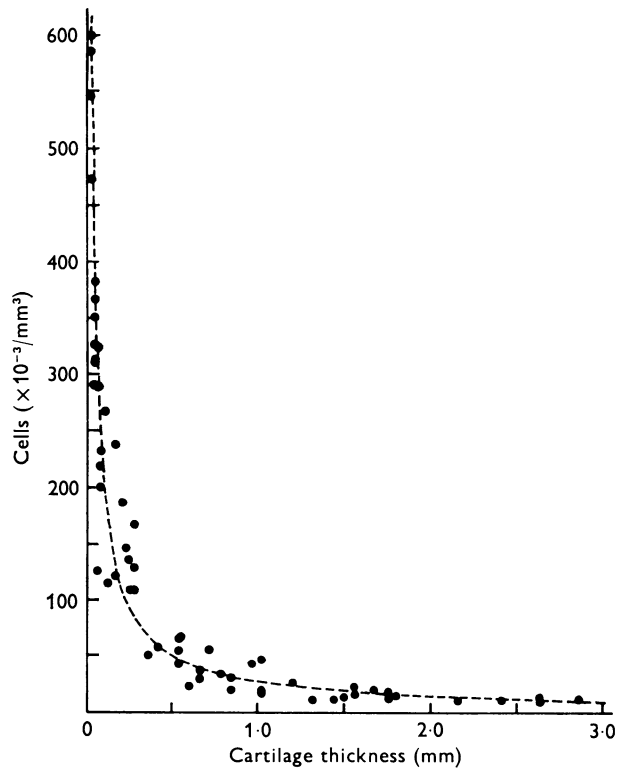


Fig. 5. Relationship of cell density to cartilage thickness. All specimens studied:  
 $y = 27\,900x^{-0.88}$ .

#### DISCUSSION

The values for cartilage thickness are in general agreement with the results of earlier workers, and complement the survey of the joints of five species made by Simon (1970). In the present investigation the knee was the joint most intensively studied, and specimens were taken from the middle region of the antero-posterior extent of the femoral condyle. This may be the reason why values given here tend to be lower than those given by Simon (1970), who measured the maximum thickness in the joint. It is improbable that the lower values can be attributed to the effects of age, since all specimens were from young adults. Furthermore, normal articular cartilage does not wear thin with age (Meachim, 1971). However, the measurements may have been affected to a slight degree by preparative artefacts and also by variations in the

level of the junction of the basal calcified cartilage with the uncalcified articular cartilage.

Cartilage thickness is related to body weight in a simple allometric manner (Simon, 1970). In the present paper the data for femoral condylar cartilage show a similar numerical relationship ( $k = 0.40$ ) to that found by Simon ( $k = 0.45$ ). Compared with quadrupeds, human cartilage is thicker than would be predicted for man's body weight. The forces acting through the human knee joint are complex and the total dynamic force varies from one to more than three times the body weight (Paul, 1967). This is unlikely to be the explanation for the thicker human cartilage, since similar high ratios of dynamic force to static load may occur in quadrupeds. In comparing man with other animals it is relevant that a quadruped bears less than one half of its body weight on its hind limbs (Simon, 1970). Accordingly, if man's body weight is adjusted to two to three times its actual amount (in Fig. 1) the value for cartilage thickness is brought into closer conformity with the quadrupedal relationship.

Estimation of the cellularity of a tissue by counting cells is not an accurate procedure. The calculation of cell density depends also on measurements of section thickness, cartilage depth and nuclear diameter which in themselves are inexact. However, the alternative procedure, DNA analysis, probably offers little advantage over the histological method in the case of small amounts of cartilaginous tissue in which there are so few cells per unit volume. Mankin & Baron (1965), working with rabbit articular cartilage, have used both methods in parallel. Their estimate of the mean quantity of DNA per chondrocyte does not differ from that for the cells of other tissues as determined by earlier workers. Hence their value for the cell density of rabbit cartilage ( $192 \times 10^3 \pm 30 \times 10^3/\text{mm}^3$ ) may be regarded as a useful standard. The comparable value found in the present study corresponds closely ( $188 \times 10^3 \pm 56 \times 10^3/\text{mm}^3$ ). Estimates of the cell content of cartilage made by workers other than Mankin & Baron are difficult to compare directly with those of the present study. In most cases this is because no correction for the effect of nuclear diameter has been made, or because different joints or species have been investigated.

It might be predicted that some relationship would exist between the cell density and the thickness of articular cartilage. The structural and functional dimensions of many organs and systems of the body are associated with the body weight and are interrelated (D'Arcy Thompson, 1968; Adolph, 1949). However, few facts have been available concerning these relationships in articular cartilage. The present study provides some information. The inverse relationship between mean cell density and cartilage thickness seems to be true for joints of different orders of size, whether from the same or from different species. Within both articular (Stockwell, 1967) and non-articular hyaline cartilage (Galjaard, 1962) the cell content decreases towards the deeper parts of the tissue. The variation in mean cell density in specimens of different thicknesses may be partly accounted for by this diminution with distance from the articular surface. However, the cell density of a superficial stratum of thick articular cartilage (for example, from the human femoral condyle) is much less than the cell density of thin articular cartilage (from the rabbit femoral condyle) of total thickness equivalent to that of the superficial stratum (see Fig. 2). Gradients of cell density within the tissue are probably related to factors which act via the articular surface,

such as nutritional supply and mechanical stresses. While the internal variation of cell density is of considerable interest, only the mean value for the whole tissue is considered in this study.

The cell number (number of cells living deep to a unit area of articular surface) appears to be remarkably constant considering the wide range of cell density and cartilage thickness observed. Differences in the cell number between very thin and thick cartilage might be diminished if the cell content of the basal calcified layer were included. This layer was excluded from measurement because it is usually very narrow with few cells; in addition the irregularity of the bone/calcified cartilage interface adds to the difficulties of cell density estimation. There are also theoretical reasons for disregarding it. In the adult it may act as an impenetrable barrier to diffusion of nourishment to the articular cartilage from the subchondral blood vessels (Maroudas, Bullough, Swanson & Freeman, 1968; Hodge & McKibbin, 1969). Recently it has been suggested, on morphological and histological evidence, that this layer should be classified as 'metaplastic bone' (Haines & Mohuiddin, 1968). Nevertheless, its inclusion in the calculation of the cell number of the cartilage would tend to elevate this value for thinner cartilage, where the layer is proportionately wider and more cellular than in thick cartilage.

It is relevant to consider factors which might influence the magnitude and the uniformity of the cell number. Among these are the nutritive requirements of the cells, and the supply of nutrient to them. For example, an equilibrium (reflected in the cell number) could exist between the rate of diffusion of glucose through cartilage and its rate of consumption by the cells. The diffusion coefficient for glucose in human femoral condylar cartilage *in vitro* has been determined experimentally (Maroudas *et al.* 1968). It has been calculated from this and the rate of glycolysis of equine carpal cartilage that the cells can be supplied with glucose via the articular surface to a critical depth of 3 mm (Bywaters, 1937; Maroudas *et al.* 1968). In most human joints the cartilage does not exceed 3 mm in thickness, suggesting that the flux of glucose into the cartilage could determine the absolute thickness and hence the cell number. However, in small joints the thickness of the cartilage may be much less than the critical depth for the supply of glucose, unless the diffusion coefficient is much lower than that in human cartilage. For example, by using the diffusion coefficient for human cartilage and the glycolytic rate of rabbit cartilage (Bywaters, 1937), it may be calculated that for rabbit femoral condylar cartilage the critical depth is well over 1.0 mm. The actual thickness of the cartilage is about 0.25 mm. In the absence of consistent data for the joint and the species, such evidence is difficult to interpret. Nevertheless it would appear that the glucose requirement of the volume of articular cartilage deep to a unit area of surface is probably about the same in all joints. This is because the mean glycolytic rate per articular chondrocyte is very similar in different species and joints (Bywaters, 1937; Rosenthal *et al.* 1941), and the cell number is also rather uniform. This conclusion in itself is of some physiological significance since it applies to joints of different size. In addition it is at least compatible with the hypothesis that nutrient requirement is a factor determining the cell number. This hypothesis could account for the deleterious effects of joint immobilization on articular cartilage (Trias, 1961; Thompson & Bassett, 1970) in all joints irrespective of their size. According to Maroudas *et al.* (1968) immobiliza-



tion *per se* can lead to a significant reduction in the diffusion coefficient because the synovial fluid becomes stagnant. This reduces the critical depth for the supply of glucose and may be damaging to the deeper chondrocytes. In rabbits, partial immobilization of the joint leads to changes in the cell density (G. Meachim, personal communication).

There is no *a priori* reason why the cell number should not vary considerably in proportion to cartilage thickness, perhaps with each cell surrounded by about the same amount of matrix in all joints. Instead, the thickness is directly proportional to the mean volume of cartilage containing one cell, probably because the mechanism of the nutrition of articular cartilage restricts the number of cells. There may be less cellular control of the tissue in thicker cartilage where the cells are widely separated. From the mechanical point of view, cartilage thickness appears to be related to the pressure-bearing functions of the joint as a whole, although it may be modified by the anatomical conformation of the articular surfaces. The compressive stress (load per contact area of cartilage) under static conditions is of the same order in a number of different joints and species (Simon, 1970). By analogy with the physical properties of rubber (Sokoloff, 1966), the greater thickness in those joints bearing a high load is presumably associated with the greater deformation which is possible in thicker cartilage. This allows a larger contact area and therefore reduces the compressive stress on the subchondral bone plate (Simon, 1970; Radin, Paul & Lowy, 1970). Since the thickness appears to be related to the requirement to spread load, the amount of matrix synthesized in the articular zone of the immature epiphysis during growth must also be related to the load. In this context, the chondrocytes could be regarded as the receptors which detect the internal stresses and strains of the tissue and react by synthesizing the necessary amount of matrix to counteract unduly large micro-stresses. It is known that cultured cells elaborate matrix when subjected to compaction (Bassett & Herrmann, 1961). It is tempting to speculate that monocilia might be involved in this mechanism; these organelles are common in immature tissue (Scherft & Daems, 1967) and have been observed in young adult human articular cartilage (Stockwell, unpublished). Alternatively, the stress on the subchondral bone plate might act as a regulator of the amount of matrix synthesized by the chondrocytes, the extent to which the subchondral vessels penetrate the bone and calcified layer and nourish the cartilage affecting the rate of synthesis. However, under experimental conditions, reduction of the load on the articular cartilage leads to increased vascularity of the subchondral bone (Thompson & Bassett, 1970) and vice versa.

The relationship of cell density and cartilage thickness may be involved in certain phenomena observed in cartilage fibrillation in degenerative states. Clusters of cells are formed at the margins of the deeper parts of the fissures, partly as a result of cell multiplication (Meachim & Collins, 1962; Mankin & Lippiello, 1970). It is possible that cluster formation might result in a restoration of the constant cell number per unit area of surface available for the diffusion of nutrients from the synovial fluid. This is difficult to quantitate in view of the complex nature of the fissuring and because of additional factors such as the changes which occur in the composition of the matrix. Certainly the cell density of the clusters is high (about  $180\text{--}600 \times 10^3/\text{mm}^3$ ) and is to a certain extent related to the distance at which the cluster apparently lies

from the edge of the fissure (Stockwell, unpublished). In any case, the evidence of the present study is in agreement with the view that cluster formation is a reaction to matrix loss (Meachim & Collins, 1962).

#### SUMMARY

1. Young adult articular cartilage from the knee joint and other sites has been investigated in eight mammalian species including man.

2. In femoral condylar cartilage of different species, the mean cell density of the uncalcified part of the tissue is variable, from 330000 cells per mm<sup>3</sup> in mouse to 14000 cells per mm<sup>3</sup> in man. Similar variation occurs in cartilage from human joints of different sizes. The thickness of the uncalcified part of the tissue in different joints also extends over a considerable range.

3. Cell density is inversely related to cartilage thickness. In all joints the number of cells deep to 1 mm<sup>2</sup> of articular surface is of the same order, averaging approximately 25000.

4. It is suggested that the number of cells deep to unit area of articular surface is related to nutritional factors, while the mean cell density of the tissue is related to the mechanical stresses on the joint.

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