THE VASCULARITY AND REMODELLING OF SUBCHONDRAL BONE AND CALCIFIED CARTILAGE IN ADULT HUMAN FEMORAL AND HUMERAL HEADS

AN AGE- AND STRESS-RELATED PHENOMENON

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A quantitative study of the vascularity and a qualitative study of the remodelling of the calcified cartilage and subchondral bone end-plate of adult human femoral and humeral heads were performed with respect to age. In the femoral head the number of vessels per unit area was found to fall 20 per cent from adolescence until the seventh decade and in the humeral head 15 per cent until the sixth decade. Thereafter an increase was noted in the femur but none in the humerus. More vessels were present at all ages in the more loaded areas of the articular surfaces: 25 per cent more for the femur and 15 per cent more for the humerus.

The degree of active remodelling by endochondral ossification declined 50 per cent from adolescence until the seventh decade in the femoral head, and 30 per cent until the sixth decade in the humeral head, rising thereafter to levels comparable to those found at young ages. More remodelling was noted in the more loaded areas at all ages.

The concept of continuous growth and remodelling, albeit slow, of the articular ends of bones is not a new one. Ogston, in 1876, remarked concerning the continuous growth of bone: "It can be seen that a group of cartilage-cells upon reaching the margin of the (subchondral) bone . . . becomes converted into one of (its) prominences". Except for the occasional remarks of observers like Heine (1926) and Harrison, Schajowicz, and Trueta (1953), this concept has mostly lain dormant until the last two decades when Johnson and others re-advanced the idea of continuous remodelling in general terms (1959) as well as in a study of the temporomandibular joint of the human adult (Moffett, Johnson, and McCabe 1962).

More recently Lemperg (1971), who studied subchondral bone plate remodelling in rabbits by micro-radiography and tetracycline labelling, demonstrated that remodelling, which occurs at a very rapid rate in immature rabbits, continues at a slower rate after the termination of longitudinal growth. In a study of the adult human patella Green, Martin, Eanes, and Sokoloff (1970) concluded that "continuous growth activity goes on in the osteochondral region during the adult years".

Changes in the activity of remodelling of the articular surface might lead to alterations in joint shape. It has recently been reported that the healthy diarthrodial joint is characterised by a physiological incongruity of

the articular surface (Bullough, Goodfellow, and O'Connor 1973). Loss with age of the incongruity which typifies the normal young adult (Bullough, Goodfellow, Greenwald, and O'Connor 1968; Goodfellow and Bullough 1968) has been reported for the hip (Bullough *et al.* 1968; Freeman 1975) and for the humero-ulnar joint (Goodfellow and Bullough 1967). Since the osteochondral ends of bone probably remodel as a result of vascular invasion and enchondral ossification of the calcified cartilage, it seemed to us that an investigation of the vascularity and remodelling of the subchondral bone and calcified cartilage might shed some light in regard to the observed age-related changes in joint incongruence.

MATERIALS AND METHODS

A total of forty-three human femoral and forty-two human humeral heads were obtained from fresh amputation specimens or cadavers ranging in age from fifteen to ninety-three years. The articular cartilage of each specimen and its respective opposing joint surface were examined grossly and found to fall within normal limits for that age group (Heine 1926). Specimens showing obvious osteoarthritis were discarded from the study. The freshly obtained specimens were for the most part examined immediately but occasionally frozen for later thawing and examination. Each specimen was assigned an arbitrary number for blind study; the code was broken only at the conclusion of the study in order to perform appropriate statistical analyses.

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Areas were defined on the surface of each femoral and humeral head to assess the vascularity and remodelling activity. These areas were such that they separated each head into portions that could be considered generally more stressed or less stressed relative to each other for the forces normally occurring through the joint. The areas were derived from reports describing the forces and patterns of loading through the hip and shoulder joints (Harrison, Schajowicz and Trueta 1953; Tobin 1955; Fessler 1957; Saha 1961; Frankel and

the counting areas on the femoral and humeral heads was not studied in order to avoid overlap and the better to segregate the different counting areas.

To study the vessels penetrating the subchondral bone end-plate and entering the calcified cartilage, the non-calcified articular cartilage was shaved off each head with a scalpel down to the layer of the calcified cartilage. Care was made not to enter into this layer but rather just to expose its uppermost surface. On the shaved surface it was then possible to see

FIG. 1

FIG. 2

Figure 1—Illustration of femoral head defining quadrants used for this study. Note cross-hatched zone between superior and inferior segments. This area was avoided in order more clearly to segregate the different portions of the head. Figure 2—Illustration of humeral head defining different segments used for this study. Note the zone between the central (C) and peripheral (P) areas. As in the femoral head, this was avoided in order better to segregate the different segments.

FIG. 3

FIG. 4

Photographs through dissecting microscope of shaved surface of a femoral head showing blood vessels in the calcified cartilage. Figure 3— $\times 9$. Figure 4— $\times 16$.

Burstein 1970; Greenwald and Haynes 1972; Greenwald and O'Connor 1972; Poppen and Walker 1976).

For counting purposes each femoral head was divided into four quadrants (Fig. 1) such that two quadrants (1 and 4) comprised the superior, relatively more stressed, segment of the head and the remaining two quadrants (2 and 3), inferior to the upper edge of the fovea, constituted the inferior, relatively less stressed, segment of the head. Each humeral head was divided into a central and a peripheral portion (Fig. 2) such that the central area comprised the relatively more stressed portion and the peripheral area the relatively less stressed part of the head. The intermediate, or boundary, zone (black cross-hatched areas in Figs. 1 and 2) lying between

small vessels coursing within the calcified cartilage. Using a Zeiss stereo zoom dissecting microscope with a net micrometer disc for counting purposes, these vessels were counted at twenty-five power (Figs. 3 and 4). Areas of uniformly filled blood vessels were sought so that accurate and reliable counts of the total number of vessels dotting the surface could be made. The same examiner (L.B.L.) counted every specimen; consequently, any error inherent in the counting method, for example, whether a dividing vessel should be counted as one or two, was averaged through the entire study. For each counting area on every head a grid area with size of 64 square millimetres was counted *in toto*; between one and six (average: four) 64 square millimetres areas were counted

within an individual segment of a head and a simple numerical average of the different counts was taken as the result for that segment. This was repeated in every counting segment for every specimen. In one specimen segments were found without areas of uniformly filled vessels and were disregarded. The results were graphed and comparisons were made between the number of blood vessels, the location on the surface of the head, and the age of the specimen.

A statistical analysis was carried out, fitting "least square" straight lines to the data. For these regression lines correlation coefficients were calculated to test the significance of the fit and, using the "t" test, confidence limits were predicted.

In order to confirm the accuracy of the vessel counts a pilot study of counting the vessels by histological means was undertaken by a different examiner (A.V.). This was done by scanning a specific number of fields at a magnification of $40\times$ in forty femoral head segments prepared for the study of the remodelling (as described below) and counting the vessels in the calcified zone. The values obtained were then compared to those obtained by the dissecting microscope counting method.

To study the activity of remodelling of the calcified cartilage by endochondral ossification a histological examination was undertaken. Each specimen, after completion of vessel counting, was divided by a bandsaw into six to ten sagittally sectioned blocks each 3 millimetres thick. The blocks containing the intermediate boundary zone were intentionally excluded in order more clearly to segregate the different portions of each head. The remaining blocks were then classified as being in the superior or inferior portion of the femoral head or the central or peripheral portion of the humeral head, fixed in formalin, decalcified in 10 per cent nitric acid, and embedded in paraffin. Six to ten sections each 5 microns in thickness were taken at different levels from the three to five blocks cut from each segment of each head. Sections were stained with haematoxylin and eosin and examined at $160\times$ magnification. Remodelling was classified as "active" or "inactive"; the criteria for this are illustrated in Figures 5 to 8.

The percentage of vessels around which "active" remodelling was occurring was calculated for each segment of each head. The results were graphed and comparisons were made between the percentage of "active" remodelling, the location on the surface of the head, and the age of the speci-

men. A statistical analysis was carried out fitting "least square" straight lines to the data. For these regression lines, correlation coefficients were computed to test the significance of the fit, and, using the "t" test, confidence limits were predicted.

RESULTS

Vascularity

Pilot study—The blood vessel counts obtained by the histological method for forty femoral segments were compared with those obtained by counting through the dissecting microscope. A graph of this comparison appears in Figure 9. The linear relationship between the values obtained by the two methods with statistical significance at the $p < .001$ level affirms the validity of using the dissecting microscope counts for the study.

Femoral head—There was no statistically significant difference between the number of vessels per unit area in either the two superior or the inferior quadrants. Consequently, all calculations were based on a simple numerical average of all the counts within either the superior or inferior half of each head. Of the heads studied, counts were successfully made for all superior portions and all but one of the inferior portions. In that one inferior portion no area of uniformly visible vessels was found, and so it was not included. Figure 10 shows that there are approximately 25 per cent more vessels per unit area in the superior portion of the head than in the inferior portion at all ages at a confidence level of $p < .001$. Inspection of these data points suggests a generally downward trend in the number of vessels per unit area from the ages of fifteen to ninety-three for both halves of the head, which is, in fact, statistically significant ($.05 > p > .02$ for "least square" straight lines fitted to each set of data). However, a more significant result is obtained when the data are analysed by division into

FIG. 5
Photomicrographs showing various stages of remodelling activity. Figure 5—Resorptive phase. Showing blood vessel, classified as "active", extending into calcified cartilage (CC) from subchondral bone (SB) actively resorbing calcified matrix. Note histological tidemark (T) above which marks upper edge of calcified zone. ($\times 250$.) Figure 6—Active bone deposition. Illustrates blood vessel within calcified cartilage surrounded by osteoblasts (O) depositing bony matrix. ($\times 250$.) Figure 7—Active bone deposition. Illustrates slightly more mature osteone than in Figure 6 with blood vessel within calcified zone surrounded by osteoblasts (O) and newly deposited bone. ($\times 250$.) Figure 8—Inactive phase. Illustrates blood vessel surrounded by mature bone within calcified cartilage. This vessel was classified "inactive" ($\times 160$.)

FIG. 9

Graph of number of vessels determined by the histological and dissecting microscope methods. Linear relationship, with significance $p < .001$, affirms the validity of the dissecting microscope method.

FIG. 11

Graph of the femoral vascularity showing the number of blood vessels per unit area plotted against age. Note both the sharp change in slope that occurs in the seventh decade and the markedly greater vascularity of the superior portion of the head.

two sets (before and after the age of sixty) and by fitting separate "least square" straight lines to the chronologically segregated data. Figure 11 shows a steady and nearly parallel decline in both portions of the head ($p < .001$) until the seventh decade when a sudden change occurs and the number of blood vessels per unit area in the calcified cartilage takes a slight, but quite definite, upward turn and then continues into old age ($p < .005$). This, too, is equally present in both the superior and inferior portions of the head.

Humeral head—Comparison of the results for the vessel counts for the two different parts of the head (Fig. 12) shows a relationship similar to that seen in the femoral head. There are approximately 15 per cent more blood vessels per unit area in the central, relatively more stressed, segment of the humeral head than in the peripheral, relatively less stressed, segment for all ages. For both segments of the head "least square" straight lines fitted to the data show a highly significant decline

FIG. 10

Display of data points showing number of blood vessels per unit area at various ages. Note that the sets of values for the superior and inferior portions comprise statistically different groups, with significance $p < .001$. "Least square" straight lines (not shown) for each set over the entire age range have downward slope and are each of significance $.05 > p > .02$.

FIG. 12

Graph of the humeral vascularity showing the number of vessels per unit area plotted against age. Note both the sharp change in slope that occurs in the sixth decade and the markedly greater vascularity of the central segment. Descending "least square" lines are of significance $p < .001$.

($p < .001$) in vascularity until the sixth decade; thereafter, a slight but insignificant increase in vascularity is seen. **Other factors**—No statistically significant correlations were found between vascularity and sex, race, or body weight.

Remodelling

Femoral head—The results obtained for remodelling activity were remarkably similar to those obtained for the vascularity in that an analogous set of relationships were noted between age, location on the head, and remodelling activity. An effort was made to survey as much of the head as possible and between 200 to 400 vessels in each half of each head were assessed. The range in percentage of remodelling activity was found to vary only slightly within either the superior or inferior hemisphere of any head.

The results (Fig. 13) show a sharp and steady fall

FIG. 13

Graph of the percentage of total vessels that are actively depositing bone plotted against age for the femoral head. $A/T \times 100$ is the number of "active" vessels divided by the total number (sum) of "active" and "inactive" vessels expressed as a percentage.

FIG. 15

Combined graph showing vascularity for both the femoral and the humeral heads. Note the greater vascularity in the femoral than in the humeral head.

of about 50 per cent in the remodelling activity from adolescence into the seventh decade. This fall was highly significant ($p < .001$) in both superior and inferior portions of the head. After the seventh decade an abrupt change occurs as the remodelling activity is seen to rise ($p < .001$). While these changes occur in both portions of the head at similar rates throughout life, remodelling activity is greater in the superior portion than in the inferior portion at all ages. Of note is the divergence in remodelling activity of the superior and inferior hemisphere at various ages. While it is small at young and old ages, the divergence is maximal in the sixth and seventh decades.

FIG. 14

Graph of the percentage of total vessels that are actively depositing bone plotted against age for the humeral head. $A/T \times 100$ is the number of "active" vessels divided by the total number (sum) of "active" and "inactive" vessels expressed as a percentage. All "least square" lines are of significance $p < .001$.

FIG. 16

Combined graph showing the remodelling for both the femoral and the humeral heads. Note the general trend of greater remodelling in the femoral than in the humeral head.

Humeral head—The results for humeral remodelling (Fig. 14) follow the same pattern as those for femoral remodelling in that the remodelling in the more stressed, central, segment is greater than the remodelling in the less stressed, peripheral, segment for all ages. A highly significant ($p < .001$) decrease in remodelling can be seen for both segments until the sixth decade, after which the remodelling is seen to rise. These changes, as well, are similar to those femoral remodelling, except that they are of a lesser degree.

Other factors—No statistically significant correlations were found between remodelling and sex, race, or body weight.

DISCUSSION

There have been two views of the function of the vessels that enter the calcified zone of the articular cartilage from the subchondral bone. On the one hand, they have been regarded as a source of nutrition to the overlying cartilage (Greenwald and Haynes 1969), and on the other hand to be concerned with remodelling of the joint surfaces through endochondral ossification. There have been a number of studies to show that these vessels play an insignificant role in nutrition of normal cartilage (Maroudas, Bullough, Swanson, and Freeman 1968; Hodge and McKibbin 1969; Honner and Thompson 1971). Their importance in subchondral remodelling is being more widely accepted (Johnson 1959; Moffett, Johnson, and McCabe 1962; Blackwood 1965; Brookes and Helal 1970; Brookes 1971; Lemperg 1971; Little 1973). If physiological joint incongruity is to be regarded as important for proper load distribution, nutrition and lubrication of the articular cartilage (Bullough, Goodfellow and O'Connor 1973), then the maintenance of the articular profile is also important. We suggest that this is accomplished by active remodelling by endochondral ossification.

Evidence has been accumulating to show the occurrence of increasing congruence of joint surfaces with advancing age, specifically, in the hip (Bullough, Goodfellow, Greenwald and O'Connor 1968), and the humero-ulnar joint (Goodfellow and Bullough 1967). This suggests that there may be a failure of some sort in the remodelling of the subchondral bone, and the results we have presented concerning age-related changes are mostly supportive of the hypothesis.

The upswing in remodelling, however, seen in older age groups is at first disconcerting in this regard. Of interest is the study of Harrison, Schajowicz and Trueta (1953) that reported hypervascularity of the bone and marked vascular invasion of the articular cartilage in osteoarthritis of the femoral head. Mankin (1974), Sokoloff (1973), and Stevens (1970) also noted increased vascularity in the femoral heads of subjects with osteoarthritis. Heine (1926), in a necropsy study of normal subjects, noted an acceleration in progressive degenerative change in the articular cartilage of the femoral head from the sixth decade on and reports an incidence of 89 per cent by the ninth decade. These reports and the concept being advanced by Mankin (1974) (Mankin and Lippiello 1970) and others (Collins and McElligott 1960; Bollet 1967) of the incipient changes of osteoarthritis as possibly being ones of proliferation and repair suggest an explanation for our findings of an increase in vascularity and remodelling for older age groups in the femoral head. Whereas there is a similar fall in the vascularity of the humeral head until the sixth decade, there is, in contrast to the femoral head, no change thereafter. In the light of this difference between femoral and humeral vascularity it is of interest to note that while the articular cartilage of human femoral heads shows increasing progressive degenerative change after

the age of sixty, the articular cartilage of human humeral heads has been reported by Heine (1926) and Meachim (1971) to show much less degenerative change with advancing age.

We also note a significant difference between the percentage of actively remodelling vessels in the more stressed and less stressed portions of the femoral and humeral heads. Why there is more remodelling in the more stressed areas of these heads than in the less stressed is uncertain. Wolff's Law (Wolff 1890) postulates that, in bone, form follows function. In general, this law is taken to apply to the distribution of the trabecular and haversian systems—that is, the internal architecture. Since the stresses across the hip joint (Tobin 1955; Fessler 1957; Frankel and Burstein 1970; Greenwald and Haynes 1972; Greenwald and O'Connor 1971) and presumably the shoulder joint (Saha 1961; Poppen and Walker 1976) are not uniform, the variations in load might be expected to be reflected in the subchondral bone and hence in the remodelling of the articular surface. The relatively more stressed portions of the femoral and the humeral head might by this reasoning have greater remodelling activity than the less stressed portions.

Composite graphs of the vascularity and the remodelling for both heads (Figs. 15 and 16) suggest another possible relationship that may exist. It can be seen that in both figures the curves of femoral vascularity and remodelling lie above those for the humeral head. Although there are no figures available comparing the load per unit area between these two joints, it is known that the magnitude of the loads through the hip in general (Frankel and Burstein 1970; Greenwald and O'Connor 1971) are greater than those through the shoulder (Saha 1961; Poppen and Walker 1976). While our findings seem to have shown that the vascularity and remodelling in the subchondral calcified zone for a joint varies according to the stresses within that joint, the possibility arises that vascularity and remodelling may also vary according to the stress between different joints.

ADDENDUM. Concerning the methods for determining blood vessel number per unit area: application of quantitative stereology was employed to design a proper analysis of the population studied, namely, blood vessels in the calcified cartilage. Accordingly the DeHoff (1967) structures that contain moderately complex gradients may have to be sampled by a set of planes that are sufficiently distributed in position to obtain a representative sample. The vessels in the calcified zone were thus sampled by planes parallel (dissecting microscope method) and perpendicular (histological method) to the surface of the calcified zone. However, a set of samples from one plane can be considered "representative" of the structure if it contains a uniform sampling of all the structural anisotropy and gradients in the population. Consequently, either sampling method could be considered "representative" if it were statistically no

different from the other, for one sample set would then confirm the other. In Figure 10 a linear relationship can be seen to exist with high significance ($p < .001$) between the two methods, demonstrating a constant identity between the two sample sets. That the slope of the line is 0.67 rather than 1.0 may well be due to the variability between the methods or to sampling error. Since the

curves drawn for vascularity and remodelling are linear, their significance is not altered by using the dissecting microscope method over the histological method. This is because the relationship between the two methods is also linear. The only difference is that the slopes for the remodelling and vascularity graphs would be slightly steeper using the histological method.

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