Who Gets Osteoarthritis and Why?

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Who gets osteoarthritis (OA)? The answer is reasonably straightforward. As concluded by Drs. Felson and Hochberg elsewhere in these proceedings[1,2], OA affects seniors, Caucasians more than Orientals, women, large people, people with greater bone density, and athletes who are at risk; and it affects them because of what they do. There is not much argument about this. However, in discussing this topic we need to define what we are speaking about: asymptomatic radiographic OA is of no interest to me — it doesn't require treatment. I'm interested only in symptomatic OA.

One of the problems in studying OA is that we include lemons and limes among the oranges. My definition of OA is simple: I differentiate OA from other forms of joint disease because of the mechanical factors involved in its development and progression. OA initially involves the loss of habitually weight-bearing articular cartilage (Figure 1). This contrasts OA with rheumatoid arthritis, lupus, and other connective tissue diseases that affect joints, in which the primary cause is inflammatory; and it is the non-weight-bearing cartilage, close to the synovium, that is initially affected.

In inflammatory arthritis the central articular cartilage becomes involved as inflammatory change progresses. In mechanically-induced OA, the non-weight-bearing articular cartilage is involved only as the joint undergoes remodeling. Also, sclerosis and thickening of the subchondral plate are hallmark features of OA, whereas juxtaarticular osteoporosis characterizes the inflammatory forms of arthritis. Statistically, the presence of osteoporosis appears to spare joints from OA.

As Dr. Burr discusses in these proceedings[3], stiffening of the subchondral bone is not a critical primary pathogenetic cause of OA, as we had thought earlier. Rather, reactivation of the primary center of ossification, thickening of the subchondral plate, and loss of habitually load-bearing articular cartilage appear to be cardinal features of the pathophysiology of OA.

Osteophytes should not be thought of as pathognomonic of OA. They occur also with other conditions. The osteophyte, indeed, is good tissue: it contains good hyaline cartilage, good bone, a good subchondral plate, and good calcified cartilage. If osteophytes are present, it is hard to believe that the cells in most of the patients with OA are sick since they can still create normal tissues.

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In short, the characteristic of OA is joint failure, driven by mechanical factors. As Felson and others have pointed out[1,2], some OA joints may not be quite right from a mechanical standpoint at the outset. The inflammatory response in OA is not primary, but secondary. Attempts to suppress inflammation in OA with nonsteroidal antiinflammatory drugs, if they are at all effective, may hasten the progression of the disease[4].

The relationship between Heberden's nodes and OA is variable. Smythe[5] established that there are several causes of Heberden's nodes, only one of which is related to generalized OA. OA affects mainly the axial skeleton and large appendicular joints. Inflammatory arthritis is very different — it can affect any joint. Interestingly, in inflammatory arthritis it is secondary mechanical changes that lead to surgery.

OA is a proliferative condition, and is characterized by an abundance of new tissue. Under these circumstances it seems inappropriate to call OA a degenerative process. New articular cartilage and new bone are being formed. The problem, of course, is that this new cartilage and new bone do not form in the right places and do not do the joint any good.

Because of its multiple etiologies, OA probably should not be considered a disease. It represents the failure of an organ (the synovial joint) and is analogous to heart failure or kidney failure. OA can begin in any of the articular or periarticular tissues. Sometimes it begins in the bone, sometimes in the cartilage, sometimes in the ligaments. Sometimes the defect lies in an abnormality in neuromuscular control. This is why efforts to identify markers of OA have proved so frustrating. The organ failure represented by OA does not begin in the same tissue in each case, and changes in one tissue within the joint are related to changes in other tissues within that organ. If changes begin in the cartilage, the bone will be altered; if changes in the bone are primary, the articular cartilage will be affected. If ligaments are damaged, everything will be affected.

When the cells are involved in joint failure, as in the rare genetically based generalized joint destruction described by Ala-Kokko, *et al*[6], in patients with a point mutation in the cDNA that codes for Type II collagen, the cartilage failure expresses itself as a mechanical problem. There are probably many genetic aberrations behind the various etiologies of OA. For example, the shape of our joints, the basic density of our bones, the way we walk and move, are all basically inherited. It is important that we begin thinking of subgroups of patients with OA. If we do not do so, epidemi-

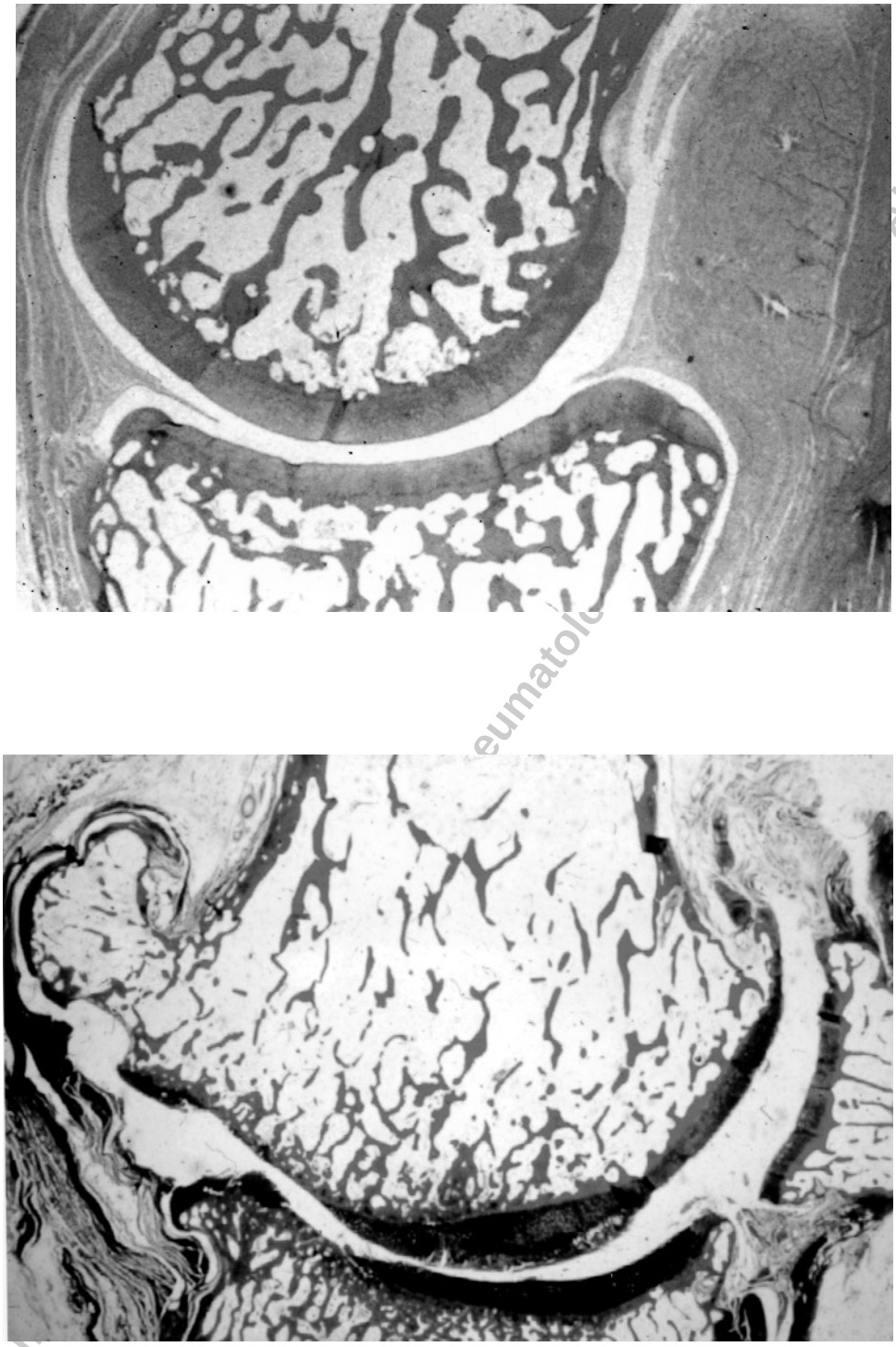

Figure 1. In OA, cartilage is lost predominantly from the habitually weight-bearing area of the articular cartilage. In other forms such as inflammatory rheumatoid arthritis and systemic lupus, non-weight-bearing cartilage at the margins of the joint, closer to the synovium, is typically affected. The top photograph depicts a histologic section of a normal distal interphalangeal joint. Note the thickness of the articular cartilage. The section view (lower photo) depicts an osteoarthrotic first metatarsophalangeal joint. Note the ulceration of the cartilage on both articular surfaces. Condensation of the subchondral bone is apparent adjacent to the areas of cartilage ulceration, and is more prominent on the phalanx than on the metatarsal head. A large osteophyte is present on the dorsal margin of the metatarsal head. (With permission from The Arthritis Foundation, Atlanta, Georgia, USA. The Revised Clinical Slide Collection of the Rheumatic Diseases, 1981.)

ologic studies will only add to our confusion. The causes of joint failure are the same as those leading to failure of other organs: congenital, developmental, post-traumatic, postinfectious.

Although increased load, such as that associated with obesity, is associated with knee OA, Maquet has suggested that the increase in thigh girth and the resultant wider-based stance alter the physiological axis of the knee joint, pushing it into varus[7]. Although a preponderance of the evidence seems to show that obesity is not associated with hip OA, Hochberg and his colleagues (see above) have challenged this[1,2].

One must agree that the affected joint tissues are excessively loaded in OA. As mentioned above, the evidence that inadequacy of joint tissues is a cause of OA seems to be based upon a small number of patients. More commonly, OA is a sequel to serious joint trauma, such as from contact sports, a fall, or a motor vehicle accident. Or the damage can be minor, but repetitive. The manner in which physiologically reasonable loads are applied is critical to the continued health of a joint. Loads that are applied too quickly damage joints and the supporting musculoskeletal structures, causing microinjury. Because these tissues are viscoelastic, they contain a water component. When these tissues are loaded, the movement of this interstitial water spares the tissue matrices from deleterious loads. If we think about what would cause damage to an extracellular matrix that contains water and proteoglycans, collagen fibers, and other molecular constituents, and we exclude circumstances that really pound on the tissue (e.g., driving into a tree or playing tackle on the football team) but consider activities of daily living, it is apparent that a damaging load must be delivered very rapidly — more rapidly than the extracellular water can be displaced. If the conditions permit water to move within the tissue, the matrix will be spared from damage. This is the beauty of viscoelasticity and the secret of viscoelastic shock absorption. Thus, in order to be damaging, loads on joints must be delivered very rapidly. If they are, they will produce microdamage, which is cumulative over time and provokes a healing response. Thus, the offending loads need not be supraphysiologic in magnitude — they merely need to be delivered too quickly.

We know that aging is associated with increasing incoordination[8]. In studies over the last 2 decades we found one in 3 adults to have micro-incoordination, a phenomenon we refer to as microklutziness[9]. Because we believe that OA is best characterized pathophysiologically by damage to the joint and attempted repair, we have hypothesized that micro-incoordination can be both a cause and a mitigating factor in the etiology of OA.

Muscles provide most of the shock-absorption for joints[9,10]. If we consider marathon runners, some grow tired by the end of the race. Their muscles are fatigued and they cannot absorb impulsive loads at heelstrike (Figure 2).

Figure 2. When periarticular muscles become fatigued as a result of overuse, they are less efficient at absorbing the impulse of load at heelstrike, a higher proportion of which is then transmitted to the joints.

However, one need not be a marathon runner to overuse the joints. When the shock absorbers fail to function effectively, the result is cumulative microdamage, leading to remodeling in the cartilage and the bone[11]. It is a little more difficult to see this in cartilage, but we believe microdamage and remodeling occur in both tissues. In which it occurs first may not be relevant. It even occurs, albeit slowly, in the calcified cartilage, where the result is enchondral ossification, leading to thickening of the subchondral plate and subsequent thinning of the articular cartilage[12]. The articular cartilage is then subjected to higher loads and undergoes fibrillation.

Reactivation of the secondary center ossification can represent either a reaction to the loss of integrity of the articular cartilage — as when there is direct acute damage to this tissue surface — or cumulative microdamage, which provokes cartilage remodeling and eventual loss of the articular surface. In both circumstances, the thickening of the subchondral plate is a critical component of the OA pathophysiology[13]. In OA the cells and their tissues are "trying to heal"[14]. However, within the biological and mechanical construct in which these tissues exist, the damage is greater than their reparative capacity.

It is important to remember that articular cartilage damage is not necessarily progressive. In a noninflammatory setting fibrillation in habitually unloaded cartilage surfaces is static. Byers, *et al*[15] and Meachim[16] illustrated this in the 1970s. To prove this point, Meachim lacerated the articular cartilage in an experimental animal under anesthesia, sewed the joint back together, and let the animal go

about its business. When he reexamined the joint some time later, there was no evidence of progression of the cartilage damage[17]. Vertical fibrillations and/or softening of articular cartilage (chondromalacia) can be nonprogressive changes (Figure 3). Arthroscopists know that this is the case in humans as well as in experimental animals.

Given that the chondrocytes are multiplying and actively synthesizing new matrix molecules at an increased rate in OA and that this disease represents joint failure at the organ level, it is important to recognize that in order to get a joint to heal we need only to surgically change the mechanical environment. Why isn't this done more often? Because it is

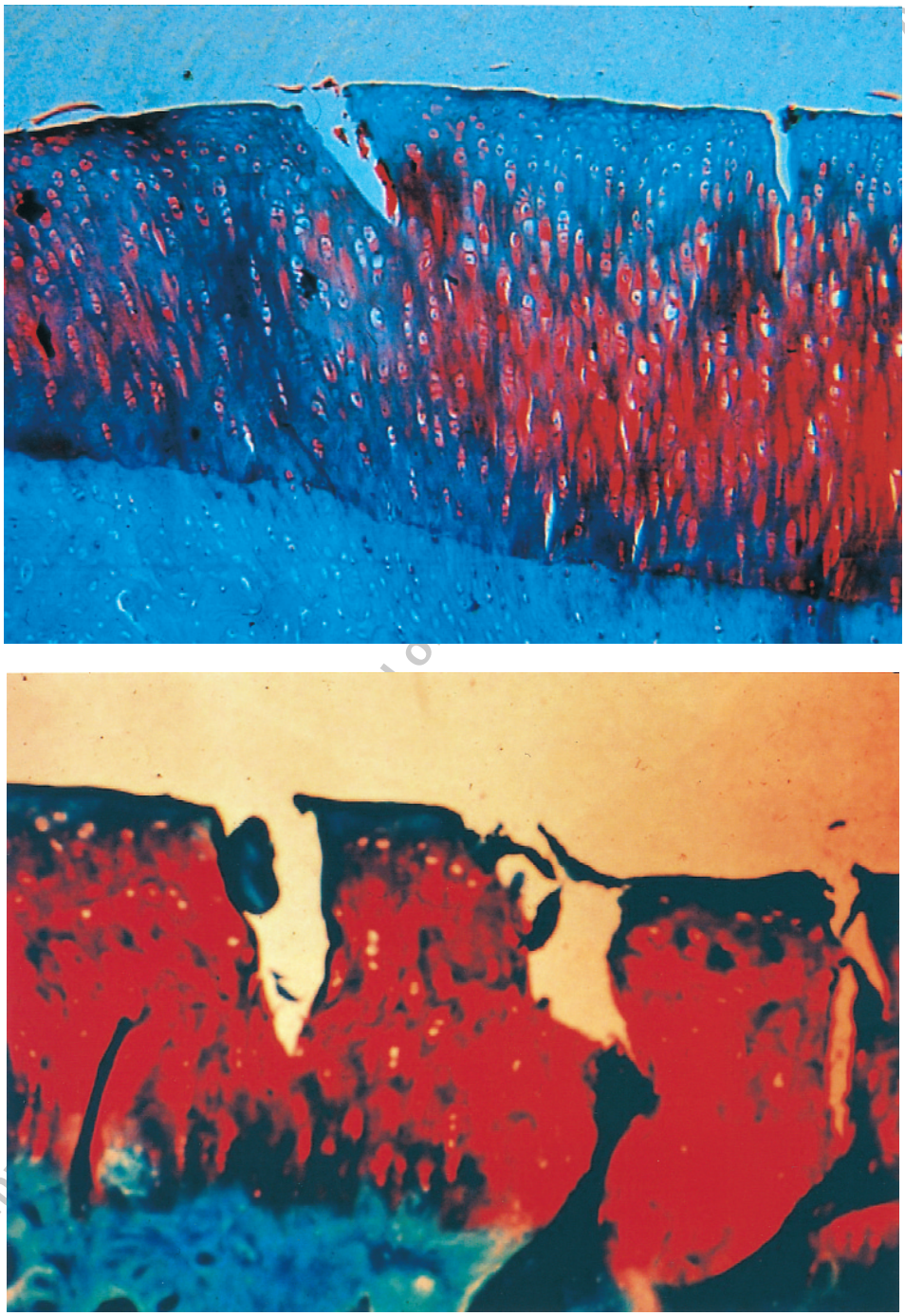

Figure 3. As shown by Meachim[17], laceration of the articular cartilage with a scalpel does not lead to progressive cartilage damage as long as the laceration does not penetrate into the subchondral bone (upper panel). A similar phenomenon is seen in humans with chondromalacia patellae, which is also nonprogressive and rarely leads to progressive damage (lower panel).

difficult. It requires precise surgery, individually tailored to each patient, and great understanding of the mechanics. It is certainly possible to reduce the amount of muscle force applied to a joint or to redistribute the stress on a joint by increasing the load-bearing area of the joint. This can be done in some patients by osteotomy or by increasing the leverage of some periarticular muscles and thus decreasing the force on the joint. A few surgeons have mastered these techniques, but they are applicable only to anatomic situations in which congruity can be maintained or reestablished (Figure 4)[18]. As for getting the patient to stop being a microklutz, we have obtained preliminary results with the use of biofeedback to train patients to reduce the rate of loading of the knee. These clinical trials are continuing in a multicenter fashion.

In osteophytes, good articular cartilage and some subchondral bone are created. Fibrocartilage, which continues to be denigrated by experts in our field, is not necessarily clinically inadequate. Patients don't mind having fibrocartilage on their articulating surfaces after an appropriate osteotomy that relieves their joint pain. The important point is to minimize any mechanical conditions that are detrimental to the cartilage and bone. It is essential that the progression of microdamage be halted. If that is done, the fibrocartilage will eventually remodel into hyaline cartilage. This, however, takes a long time. A number of studies have now been reported by arthroscopists who have performed cartilage biopsies after a successful osteotomy and shown that fibrocartilage may persist for years[19].

The causes of OA are multifactoral and heredity is obviously involved. Whether an individual develops valgus or varus knees depends on her genes. Whether he or she is a microklutz may also depend on her genes. However, except in certain subgroups, the gene story is confusing. Heredity can be responsible for congenital as well as for developmental anatomic abnormalities.

So, who gets OA and why? Older individuals who have acquired cumulative microdamage have less effective shock-absorbing mechanisms due to the loss of proprioceptive acuity with age. On the other hand, OA sometimes develops in young adults with congenital abnormalities or in those who have had significant joint trauma or infection. All abnormal joints, however, do not become arthrotic. In the Iowa studies[20] of men and women who had hip dysplasia, slipped capital femoral epiphysis, or Legg-Calvé-Perthes disease as children, the penetrance of OA in a longterm followup was not 100% but more like 60–70% at 30 years. The penetrance of OA would appear to depend upon the mechanical condition in which the joint exists. Anyone with a congenital or developmental abnormality or post-traumatic or postinfectious joint abnormalities has a joint that is at increased risk of developing OA. All of these conditions can result in the concentration of mechanical stress on the articular surface. Individuals who accumulate too much microdamage from repetitive unprotected impulsive loading are also at risk. Age, race, sex, load, and trauma are all important etiologic factors and can be interrelated, making epidemiologic study of this disease very confusing. We

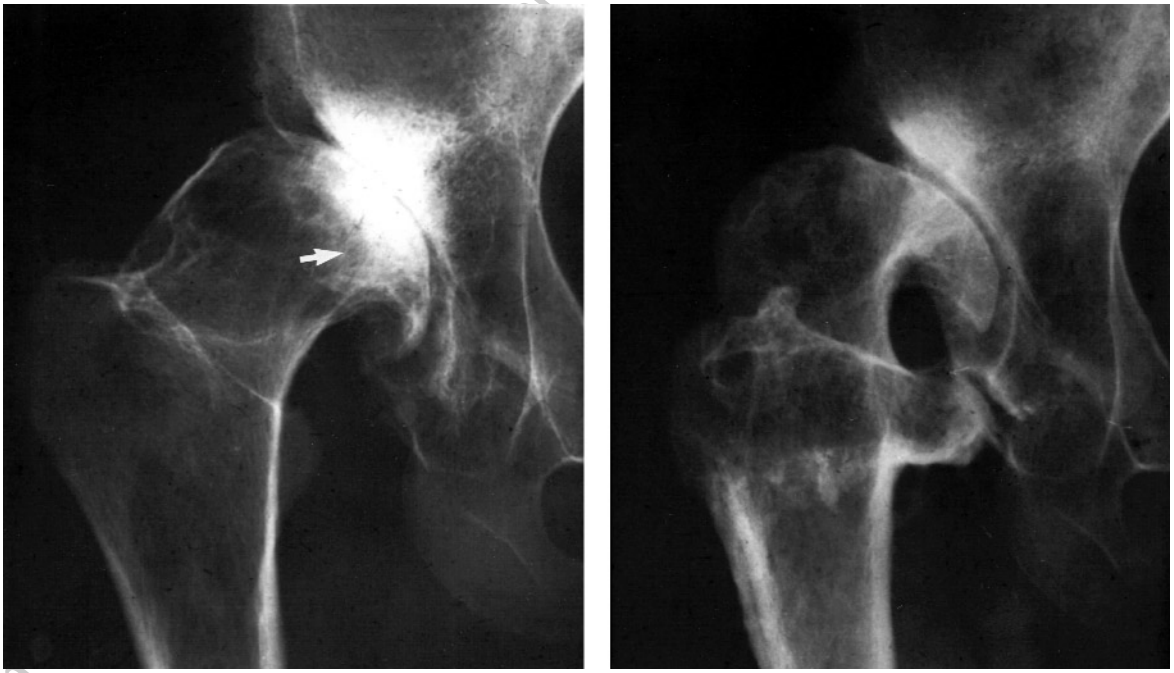

Figure 4. Radiographs of a 36-year-old woman with hip dysplasia that led to OA. Left panel shows a radiograph obtained prior to osteotomy. Right panel shows the same hip 7 years after a successful osteotomy. During surgery, the alignment of the femur was altered so that the large beak osteophyte (arrow) was shifted to the weight-bearing region of the joint. Note the striking decrease in subchondral sclerosis and regrowth of the joint space after surgery.

suggest that our understanding of OA can be improved in the future by looking closely at individual subgroups.

In summary, if we are going to treat OA nonoperatively, joint loading, anatomy, and alignment count. Total joint arthroplasty is a procedure that represents the abject failure of medical management but, fortunately, is available and has made many patients more comfortable. Joints can heal if we can determine how to return habitually loaded contact areas to conditions of normal stresses and rates of loading. Joint motion is important because it induces the metaplasia of cells to produce the kinds of tissue we want in the joint[21]. By contrast, without movement, cartilage atrophies[22].

Figure 4 shows a successful hip osteotomy 7 years after surgery. During the procedure the medial teardrop osteophyte was shifted into the weight-bearing area, increasing its surface area. Even with a larger weight-bearing area, the hip abductor muscles had to be lengthened to assure an adequate decrease in intraarticular stress[23]. As a result, this patient's pain has subsided, the subchondral sclerosis that was present initially has receded, and the joint space has reappeared. The major point: after a well done osteotomy the patient's joint pain — which isn't apparent radiographically but arises from synovial inflammation or from the subchondral bone — can disappear.

When we operate on late stage OA, there may be no evidence of inflammation, but only a very thick capsule and synovium. Trabecular microfracture, although it does not cause stiffening of the bone, may, if sufficiently widespread, be a significant factor because it obliterates the intertrabecular channels, thereby increasing the intraosseous pressure. As with any tissue damage, this is a trigger for remodeling and reactivation of the secondary center of ossification. The pathophysiologic importance of trabecular microfracture in reactivation of the secondary center of ossification and subchondral thickening in OA cannot be overemphasized.

Osteotomy can achieve a very satisfactory result in certain joints, but it is important to know in which joint this will be the case. As shown in Figure 4, it is very important to realign the joint, to bring the teardrop exactly into what we can predict will be the load-bearing area. Osteotomy is exacting surgery, performed in the operating room with protractors. For good results, the surgeon must come within 1° to 2° of his objective. The operation must be planned and individualized for the pathoanatomy of each patient. Because of the variations in pathoanatomy, not every patient is a suitable candidate for osteotomy. This is why total joint replacement is so popular — it is a much easier procedure than osteotomy and, unlike the latter, is applicable to almost all patients with OA.

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