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# The Association of Bone Marrow Lesions with Pain in Knee Osteoarthritis

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Background: **The cause of pain in osteoarthritis is unknown. Bone has pain fibers, and marrow lesions, which are thought to represent edema, have been noted in osteoarthritis.**

Objective: **To determine whether bone marrow lesions on magnetic resonance imaging (MRI) are associated with pain in knee osteoarthritis.**

Design: **Cross-sectional observational study.**

Setting: **Veterans Affairs Medical Center.**

Patients: **401 persons (mean age, 66.8 years) with knee osteoarthritis on radiography who were drawn from clinics in the Veterans Administration health care system and from the community. Of these persons, 351 had knee pain and 50 had no knee pain.**

Measurements: **Knee radiography and MRI of one knee were performed in all participants. Those with knee pain quantified the severity of their pain. On MRI, coronal $T_2$-weighted fat-saturated images were used to score the size of bone marrow lesions, and each knee was characterized as having any lesion or any large lesion. The prevalence of lesions and large lesions in persons with and without knee pain was compared; in participants with knee pain, the presence of lesions was correlated with severity of pain.**

Results: **Bone marrow lesions were found in 272 of 351 (77.5%) persons with painful knees compared with 15 of 50 (30%) persons with no knee pain ($P < 0.001$). Large lesions were present almost exclusively in persons with knee pain (35.9% vs. 2%; $P < 0.001$). After adjustment for severity of radiographic disease, effusion, age, and sex, lesions and large lesions remained associated with the occurrence of knee pain. Among persons with knee pain, bone marrow lesions were not associated with pain severity.**

Conclusions: **Bone marrow lesions on MRI are strongly associated with the presence of pain in knee osteoarthritis.**

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**See editorial comment on pp 591-593.**

Knee osteoarthritis affects 11% to 15% of the U.S. population 65 years of age or older (1) and is a leading cause of disability in the elderly. The major source of disability and care seeking for patients with osteoarthritis is pain in the knee (2).

The cause of knee pain in patients with osteoarthritis is unclear. Osteoarthritis has been considered a disease whose characteristic pathologic feature is loss of hyaline articular cartilage, but that tissue contains no pain fibers. Pain fibers are present in several other structures, however, that are often affected by pathologic processes in knee osteoarthritis, including the joint capsule, ligaments in and around the knee joint, the outer third of the meniscus, and possibly the synovium (although for this last tissue, evidence is conflicting [3, 4]). In addition, bone in the periosteum and bone marrow is richly innervated with nociceptive fibers and represents a potential source of pain in patients with knee osteoarthritis.

In athletes and younger adults who do not have osteoarthritis, traumatic knee injuries produce high-signal lesions in the medullary space extending to subcortical bone according to $T_2$-weighted magnetic resonance imaging (MRI). These lesions are thought to represent contusions within the bone marrow and have been correlated with the occurrence of pain in athletes (5). Bone marrow lesions that are similar in appearance to those contusions have been noted (6) in patients with knee osteoarthritis, but their association with the occurrence of pain in this disease is unknown.

The treatment of pain in osteoarthritis has been frustrating, in part because the target of therapy is unclear. Creamer and colleagues (7) injected intra-articular anesthetic into joints and found that only 6 of 10 persons with painful osteoarthritis had pain relief. This suggests that in some patients, pain originates from extra-articular, noncapsular sources, one of the most likely of which is bone. If pain in some patients does emanate from bone, this finding would have important therapeutic implications and suggests that for these patients, anti-inflammatory treatments targeted at synovitis or intra-articular drainage to relieve capsular distention would be ineffective.

We sought to evaluate whether persons with knee pain and osteoarthritis were more often affected by bone

marrow lesions than similarly aged persons without knee pain, many of whom also had radiographic knee osteoarthritis. We tested whether pain in the knee was associated with the presence of bone marrow lesions after adjustment for the severity of radiographic osteoarthritis. In addition, among persons with symptomatic knee osteoarthritis, we evaluated whether the severity of their pain was associated with the presence of these lesions.

## METHODS

### Patient Selection

The minimum age for entry into the study was 45 years for men and 50 years for women. The entry age for women was chosen to lessen the chance of inadvertently obtaining radiographs in pregnant women. Male participants were drawn from the Veterans Health Study (VHS), a prospective observational study of health outcomes in 2425 veterans (8). Participants in the VHS were recruited from all men receiving ambulatory care between August 1993 and March 1996 at four Veterans Administration system facilities in the Boston area. Veterans who indicated that they could not read, were identified as unable to answer questions by an accompanying proxy, were disoriented, or did not complete the screening questionnaire were ineligible.

A random sample of eligible respondents was contacted by telephone and recruited for the VHS. Of the 4137 patients who were telephoned, 2425 (59%) participated in the VHS. Participant age ranged from 22 to 91 years (mean, 62.4 years). The VHS was designed to be representative of users of ambulatory care in the Veterans Administration system. Compared with all utilizers of the Veterans Administration health care system, the sample underrepresented patients with less education or limitations in literacy or cognitive functioning. Patients in the VHS had lower functional status scores on the physical and mental health components of the Short Form-36 survey (a measure of health status) and had more comorbid conditions (8) than do men 45 years of age or older in the general U.S. population. Male participants were also drawn separately from Veteran Affairs clinics and from the community.

Female participants were drawn from clinics at Boston Medical Center and the Veterans Affairs Medical Center; from advertisements in local newspapers; and from a study of women veterans, the Veterans Administration Women's Health Project ($n = 719$), that was designed to describe the health status of female veterans using ambulatory health care services. The human studies committee and the institutional review board approved protocols. Informed consent was obtained from all participants.

All participants were surveyed about knee symptoms. They were asked two questions: "Do you have pain, aching, or stiffness in one or both knees on most days?" and "Has a doctor ever told you that you have knee arthritis?" For persons interested in participating in our study of knee pain and osteoarthritis, we conducted a follow-up interview in which those who answered "yes" to both questions were asked about other types of arthritis that could cause knee symptoms. If no other forms of arthritis were identified in the interview, the person was eligible for recruitment as a participant with knee pain (which we characterize here as knee symptoms).

**Figure 1** is a flow diagram of the source of participants. Of our male participants, 151 came from the Veterans Health Study, 76 came from Veterans Administration ambulatory clinics, and 8 came from the community. Of our female participants, 18 came from the Veterans Administration Women's Health Project, 9 came from ambulatory clinics, and 89 came from the community.

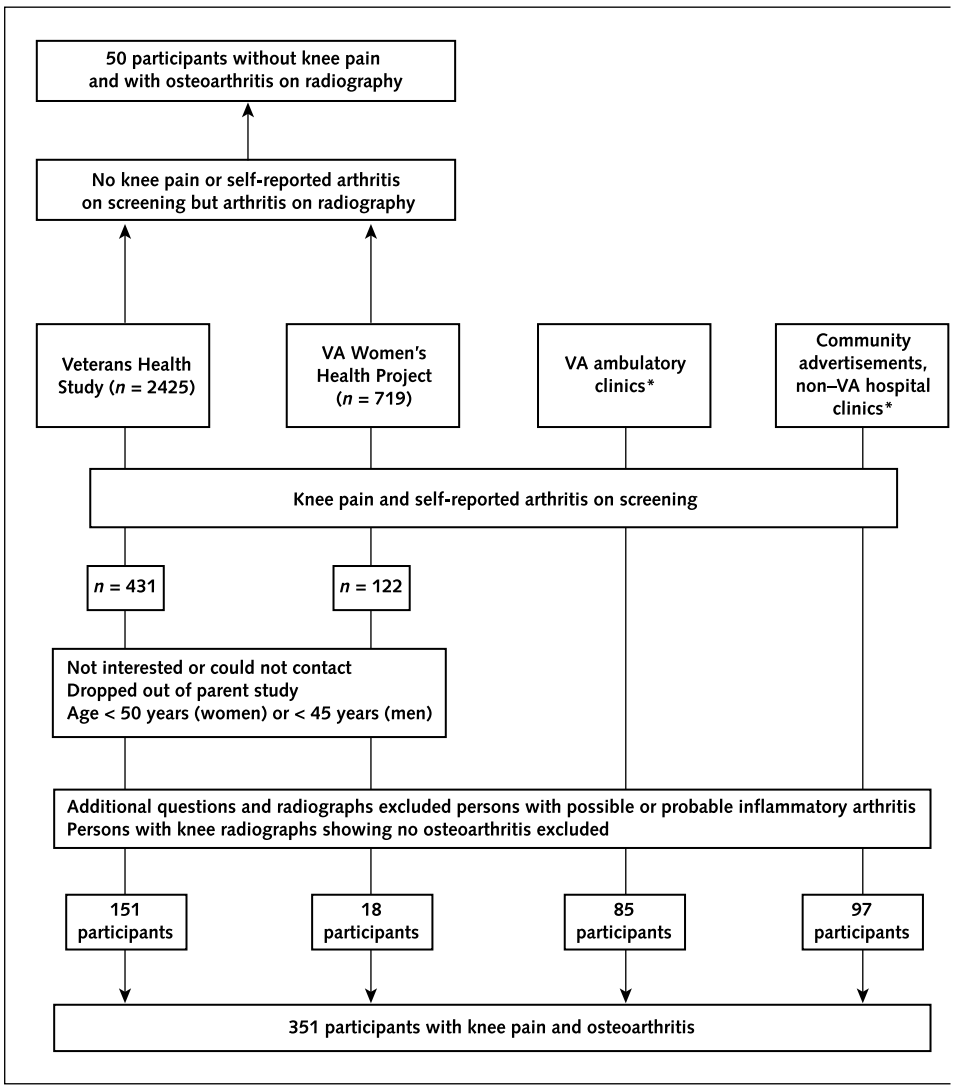
We recruited participants from the VHS and the Veterans Administration Women's Health Project without knee pain from among those who answered "no" to both of the above screening questions (**Figure 1**).

We also asked participants to evaluate the severity of pain in each knee, which they scored by using a 100-mm visual analogue scale (generating a score of 0 [no pain] to 100 [most severe pain possible]). Participants also filled out the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) questionnaire (9), a validated instrument that assesses knee pain and disability during various activities; we analyzed their WOMAC pain subscale score.

### Radiographic Evaluation

All participants underwent weight-bearing posteroanterior radiography by using the protocol of Buckland-Wright (10 and weight-bearing skyline (9) and weight-bearing lateral radiography (11). For the posteroanterior view, the knee was positioned and radio-

*Figure 1.* **Sources of study participants.**




VA = Veterans Administration.

graphed under fluoroscopy so that the anterior and posterior medial tibial plateaus were superimposed; this was done to optimize measurement of joint space. Radiographs were read for the presence of definite osteophytes and other features by one radiologist using an atlas.

If a definite osteophyte was present in a knee (including the patella) on any one of the three views, the knee was characterized as having osteoarthritis regardless of whether the participant experienced symptoms. This definition of radiographic disease has been recommended by other investigators (22). On the basis of responses to the screening questions, we defined a knee as symptomatic if the participant stated that he or she had pain or aching in that knee on most days. This definition of symptomatic osteoarthritis meets American College of Rheumatology criteria (12). We identified too few symptomatic persons without a radiographic osteophyte to include them as a separate study group ($n = 4$) and therefore excluded them; we also excluded 16 participants without knee pain whose radiographs showed no osteophytes.

Kellgren and Lawrence grades have been developed for the anteroposterior (posteroanterior) view. We therefore assigned Kellgren and Lawrence grades (0 to 4) on

this view only. In addition, we read posteroanterior, skyline, and lateral radiographic views and scored them for individual radiographic features—osteophytes (scale of 0 to 3), joint space narrowing (scale of 0 to 3), cysts (scale of 0 to 1), and sclerosis (scale of 0 to 3)—by using the Framingham Osteoarthritis Study atlas (13). The reproducibility of readings of these features and of the Kellgren and Lawrence scale is reported elsewhere (14).

### Magnetic Resonance Imaging

Each person with knee pain underwent MRI of the more symptomatic knee. For persons without knee pain, the dominant knee was selected for imaging. All studies were performed on a General Electric Signa 1.5-Tesla MRI system (GE Medical Systems, Milwaukee, Wisconsin) using a phased-array knee coil. A positioning device for the ankle and knee was used to ensure uniformity between patients. Coronal, sagittal, and axial images were obtained in each participant. Coronal spin-echo fat-saturated proton-density and $T_2$-weighted fat-saturated images (repetition time, 2200 ms; echo time, 20/80 ms) with a slice thickness of 3 mm, a 1-mm interslice gap, 1 excitation, a field of view of 11 to 12 cm, and a matrix of $256 \times 128$ pixels were obtained.

To evaluate bone marrow lesions on MRI, we used coronal spin-echo $T_2$-weighted fat-saturated images. Each femur and tibia was divided into medial, central, and lateral quadrants, resulting in six potential sites of lesions in each knee. We defined bone marrow lesions as discrete areas of increased signal adjacent to the subcortical bone in either the femur or the tibia, and we scored each bone marrow lesion from 0 to 3 on the basis of lesion size (**Figure 2**). Lesions with a score of at least 1 were considered definite bone marrow lesions, and lesions with a score of at least 2 were considered large bone marrow lesions.

We mixed MRIs of participants with and without knee pain and blinded the reader to the participants' knee pain status. Overall, intraobserver agreement for bone marrow score was a weighted $\kappa$ value of 0.66 (95% CI, 0.59 to 0.72), which indicates substantial agreement beyond chance (15). We also scored knee MRIs for effusions on a scale of 0 to 4 on the basis of effusion size (16).

### Statistical Analysis

We studied one knee per participant, and our unit of analysis was the knee. Preliminary analyses revealed that when we added lesion scores from all quadrants, the summed score clustered in the lower end of the range, with none exceeding 9; 75% of the knees had scores of 2 or less. To simplify analyses and because we hypothesized that single bone marrow lesions, especially large ones, would be associated with knee pain, we decided to evaluate knees as not having or having bone marrow lesions (any score $\geq 1$) and to evaluate knees with and without large bone marrow lesions (any score $\geq 2$). We compared the prevalence of bone marrow lesions and large bone marrow lesions in persons with symptomatic knee osteoarthritis with those in persons without pain by using chi-square or the Fisher exact test where appropriate.

To evaluate whether pain was associated with the presence of bone marrow lesions, we adjusted for radiographic severity because participants with symptomatic osteoarthritis had greater severity of structural disease than did those without pain. We restricted the group with knee symptoms to persons whose Kellgren and Lawrence grades or scores for individual radiographic features were in the same range as those of participants without knee pain (scores of 1 to 5 for individual radiographic features). The individual radiographic features score sums the scores for presence of all osteophytes, narrowing, cysts, and sclerosis on any of the three views. We used this score to provide more detail on radiographic severity and to incorporate radiographic features seen on views other than the posteroanterior.

Because the literature suggests an association of capsular distention with knee pain and because we found an association of effusion with knee pain in this sample (16), we performed analyses with adjustment for the size of the knee effusion. We performed logistic regression analyses to test the association between bone marrow lesions (an independent variable) and knee pain (a dichotomous dependent variable), after adjustment using forced entry for the following independent variables: radiographic severity (sum of the scores of individual radiographic features), age, sex, and effusion score. We performed identical analyses for bone marrow lesions (yes or no) and large bone marrow lesions (yes or no). In similar analyses incorporating body mass index, results were unchanged.

We next evaluated whether, among persons with symptomatic knee osteoarthritis, those with bone marrow lesions experienced more severe pain than those

without such lesions. For each bone marrow and large bone marrow lesion, we performed two different linear regression analyses. In one analysis, the dependent variable was score on the visual analogue scale for pain in the knee, and in the other, it was the WOMAC subscale score for knee pain. We included the following independent variables by using forced entry: presence or absence of bone marrow lesions, sum of the scores of individual radiographic features, sex, age, and effusion score.

### Role of the Funding Sources

This research was supported by Bayer Corp., the Arthritis Foundation, and the National Institutes of Health. None of these agencies had a role in the design, conduct, or reporting of this study.

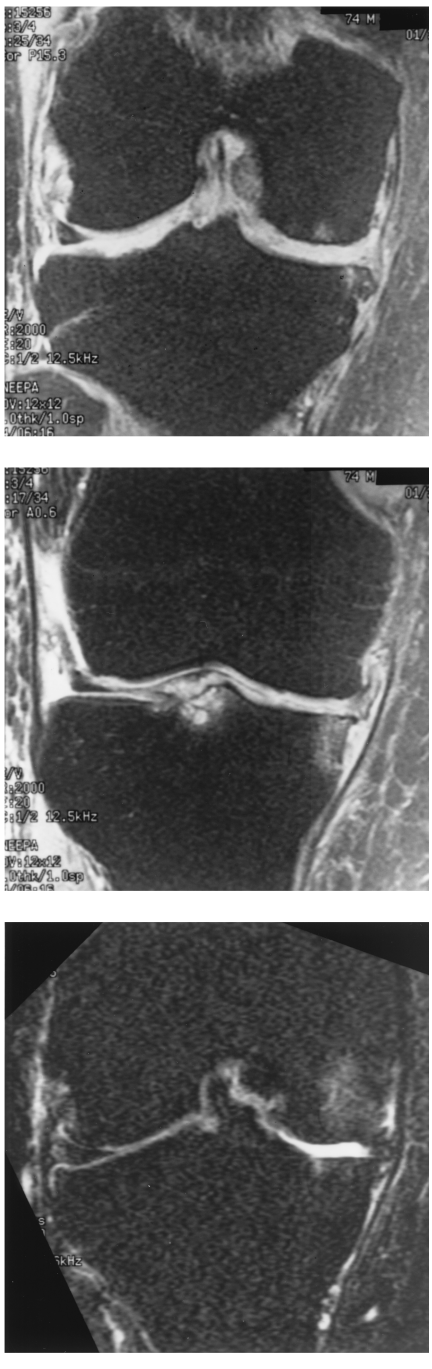
## RESULTS

We studied 351 participants who had knee pain and 50 participants who had no knee pain. All participants had evidence of osteoarthritis (at least a small osteophyte) on radiography. The mean age was 66.8 years in participants with knee pain and 66.9 years in those without knee pain (**Table 1**). Participants with knee pain had higher Kellgren and Lawrence grades on the posteroanterior radiograph than did those without knee pain. The range of grades varied considerably, and some participants with knee pain had grades of 0 (because the Kellgren and Lawrence grade was scored on the posteroanterior radiograph only and did not reflect disease in the patellofemoral joint).

Of participants with knee pain, 77.5% had MRI evidence of a bone marrow lesion compared with only 30.0% of participants without knee pain ($P < 0.001$). Even more striking was the difference in the prevalence of large bone marrow lesions between participants with knee pain and those without knee pain (35.9% vs. 2.0%; $P < 0.001$) (**Table 2**).

We speculated that bone marrow lesions may be highly correlated with the severity of radiographic disease, which differed substantially between participants with and those without knee pain. Therefore, we looked within each Kellgren and Lawrence grade at the prevalence of bone marrow lesions, comparing participants with knee pain with those without it. Within each Kellgren and Lawrence grade, the prevalence of bone marrow lesions in painful knees differed substantially from

*Figure 2.* **Grades of bone marrow lesions.**



**Top.** Two grade 1 lesions beneath the medial femoral condyle and medial tibial plateau. Both lesions were seen on one adjacent slice. **Middle.** Grade 2 lesion beneath the medial tibial plateau. This particular lesion was seen on three adjacent slices. **Bottom.** Grade 3 lesion beneath the medial femoral condyle, seen on four adjacent slices. Small grade 1 lesions (which still sum to a grade 1 lesion on the basis of the total volume of lesions) on the medial tibial plateau are also visible.

*Table 1.* **Participant Characteristics**

| Characteristic | Knee Pain and Osteoarthritis ($n$ = 351) | No Knee Pain and Osteoarthritis ($n$ = 50) | $P$ Value* |
|---|---|---|---|
| Women, % | 33 | 48 | 0.04 |
| Mean age ± SD (range), *y* | 66.8 ± 9.3 (47–91) | 66.9 ± 8.5 (47–85) | >0.2 |
| Mean body mass index ± SD (range), $kg/m^2$ | 31.6 ± 5.8 (19–60) | 28.8 ± 4.7 (18–37) | 0.01 |
| Median Kellgren and Lawrence grade of studied knee (range) | 2 (0–4) | 0 (0–2) | <0.001 |
| Mean sum of individual radiographic features ± SD (range)† | 6.1 ± 4.2 (0–21) | 1.4 ± 1.5 (0–5) | <0.001 |

* Chi-square test.
† The individual radiographic feature score of studied knee consisted of total of osteophyte, narrowing, sclerosis, and cyst scores on all views.

that in nonpainful knees. In addition, bone marrow lesions were more frequent in those with higher grades of radiographic disease. Among participants with knee pain, the prevalence of lesions ranged from 48% of knees (30 of 63) with Kellgren and Lawrence grades of 0 to 100% (15 of 15) of those with Kellgren and Lawrence grades of 4.

When we restricted our evaluation to the presence of large bone marrow lesions, we found a substantial prevalence of such lesions among participants with knee pain; this prevalence increased with increasing Kellgren and Lawrence grade. Of participants without knee pain, almost none had large bone lesions; among knees with Kellgren and Lawrence grades of 0 and 1, the difference in prevalence between participants with (16 of 129 [12.4%]) and without knee pain (0 of 38 [0%]) was substantial.

We evaluated whether bone marrow lesions were statistically more prevalent in participants with knee pain than in those without knee pain after adjustment for other factors that may contribute to knee pain. We restricted these analyses to participants who had relatively low Kellgren and Lawrence grades (0 to 2) because no participant with a painless knee had a Kellgren and Lawrence grade greater than 2. Thus, 221 participants with knee symptoms were analyzed. Forty-seven participants without knee pain were included in the analysis; three high-quality radiographic views were available for each, which made it possible to generate a score for individual radiographic features. When we adjusted for overall scores of individual radiographic features, effusion score, sex, and age, we found that bone marrow lesions were associated with the presence of knee pain (odds ratio, 3.31 [95% CI, 1.54 to 7.41]). Using the same analytical approach, we focused on large bone marrow lesions and found that large lesions were also strongly associated with the presence of pain (odds ratio, 5.78 [CI, 1.04 to 111.11]). Results were similar when we used Kellgren and Lawrence grade as our measure of radiographic severity instead of score for individual radiographic features.

Finally, we tested whether the presence of bone marrow lesions or large bone marrow lesions was associated with a greater severity of knee pain. We analyzed 243 knees with symptomatic osteoarthritis, for which we had information on all model variables. Compared with knees that did not have bone marrow lesions, the presence of lesions was associated with a 7.8-mm higher average pain score (range, 0 to 100 mm) (CI, −1.1 to 16.7 mm; $P = 0.08$), whereas the presence of large lesions (compared with no large lesions) was associated with a 2.6-mm higher average pain score (CI, −4.3 to 9.5 mm; $P > 0.2$). Results were similar when the WOMAC pain score was used.

*Table 2.* **Bone Marrow Lesions in Participants with and without Knee Pain**

| Finding | Knee Pain and Osteoarthritis | No Knee Pain and Osteoarthritis | $P$ Value |
|---|---|---|---|
| | *n (%)* | | |
| Bone marrow lesion | 272 (77.5) | 15 (30.0) | <0.001* |
| Large bone marrow lesion | 126 (35.9) | 1 (2.0) | <0.001† |

* Chi-square test.
† Fisher exact test.

## DISCUSSION

Our results show that bone marrow lesions in knees are associated with the most important symptom of osteoarthritis: pain. Bone marrow lesions were much more prevalent in participants with knee pain than in those without it. This association could not readily be explained by such confounders as severity of radiographic

disease and presence of effusions, another potential cause of pain. Thus, our results suggest that bone marrow lesions contribute to the occurrence of pain in persons with knee osteoarthritis. In participants with knee pain, we found no association between presence of these lesions and severity of pain.

Several caveats are in order. First, our results are cross-sectional, and any relation between bone marrow lesions and pain should be corroborated in a longitudinal study. Second, our comparisons of persons with and without knee pain were restricted to persons with relatively mild radiographic severity, because no one in the group without knee pain had severe radiographic disease. The lack of pain-free participants with more severe radiographic osteoarthritis precluded us from estimating the specificity of bone marrow lesions for absence of knee pain. Our results may therefore not be generalizable to persons with more severe radiographic disease.

Our separate analyses of bone marrow lesions (any lesion $\geq$ grade 1) and large lesions (any lesion $\geq$ grade 2) are not independent of one another. If a Bonferroni correction because of nonindependence were performed, each comparison of participants with pain and those without pain would remain statistically significant at a $P$ value less than 0.001.

Our failure to find an association of bone marrow lesions with severity of pain in persons with knee pain suggests that such pain stems from many causes. Other potential causes of knee pain include capsular distention from large effusions and synovitis. Any given cause (for example, bone marrow lesions) may not produce worse knee pain than any other one (for example, capsular distention).

The involvement of bone in the pathologic process of osteoarthritis has been neglected. Recent evidence suggests that juxtaarticular lesions on bone scintigraphy, similar to the bone marrow lesions that we observed, identify persons with osteoarthritis who are at high risk for progression (17). Thickening of the superficial subchondral plate may be separable from deeper pathology, which the bone marrow lesions we describe may represent.

Histologically, these bone marrow lesions generally reflect pathologic evidence of increased water, blood, or other fluid inside bone, such as might occur with localized edema or contusions. Information on other painful regional musculoskeletal disorders supports our contention that bone marrow lesions are associated with pain. In addition to the example of athletes with bone contusions (5), in a recent report of 37 patients with hip osteonecrosis, a striking association was observed between bone marrow edema lesions on MRI and pain (18). Bone marrow edema lesions occurred in 50% (7 of 14) of persons with pain but in only 4% (1 of 23) without pain. Furthermore, resolution of pain coincided with the disappearance of marrow edema. Similar findings on MRI typify a syndrome called "transient painful osteoporosis" (19). Patients with this syndrome present with a painful joint and have similar bone marrow lesions on MRI, but radiography is usually normal. Since osteoporosis has not been documented in these patients, some investigators (19) have suggested that the syndrome be renamed "the transient marrow edema syndrome."

In work that may be related to ours, Arnoldi and colleagues (19) reported that patients with knee and hip osteoarthritis often have intraosseous hypertension due to poor venous drainage from the marrow. Such patients had positive technetium phosphate bone scans, a finding that correlates highly with bone marrow lesions on MRI (20). The researchers suggested that this intraosseous hypertension caused joint pain and reported that fenestration of the bony cortex and osteotomy both reduced this hypertension.

The reproducibility of our bone marrow lesion readings was substantial ($\kappa = 0.66$) although not high. We believe that scoring MRIs is inherently more difficult and likely to produce lower levels of reader agreement than scoring radiographs, because readers must score the size of lesions spread over multiple image slices. Other investigators have reported $\kappa$ values for reliability in reading knee MRIs that were substantially lower than ours, generally 0 to 0.4 (21). Even though we provided guidelines to accomplish this task, it remained challenging. In addition, our method of testing reliability was to standardize the reader according to the atlas, ask them to read the sample of films (which took more than 1 year), and test the reliability on a random sample of the films they had read, some of which were read 1 year before. This results in an observer agreement value that is realistic but tends to be lower than values obtained when reliability is measured in one session or two sessions close in time.

In conclusion, persons with knee pain and osteoarthritis more often have lesions on MRI suggestive

of bone marrow edema than do persons with a similar degree of radiographic osteoarthritis but without knee pain. In persons with knee pain, these lesions were not associated with severity of pain. Our results suggest that bone marrow lesions may contribute to the central disabling feature of osteoarthritis: pain.

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"Do you understand me, child?"

"Of course," she said. "Why shouldn't I?"

"It surprises you that I say the blood circulates through the body, no doubt?"

"That could only surprise a physician," she said. "Any farmer knows it."

"How do you mean?"

"If you bleed a pig, you cut the main vein in its neck. The pig bleeds to death and produces soft white meat. How else could all the blood come out of one slit unless it was all connected? And it moves of its own accord, almost as though it is being pumped, so must go round and round. That is all obvious, isn't it?"

I blinked, and stared at her. It had taken practitioners of the medical art the better part of two thousand years to make this astounding discovery, and there was this girl saying she knew it all along. A few days ago, I would have been furious at her impudence. Now I merely wondered what else she—and the country folk she mentioned—might know if only people troubled to ask them.

Iain Pears
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